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FORUM REVIEW ARTICLE

FORUM TOPIC: **REACTIVE OXYGEN, NITROGEN AND SULFUR**FORUM EDITOR: **LAURENT CHATRE****The Reactive Species Interactome in the brain**Elise Malard¹, Samuel Valable¹, Myriam Bernaudin¹, Elodie Pérès¹, Laurent Chatre¹¹Normandie Univ, UNICAEN, CEA, CNRS, ISTCT/CERVOxy group, GIP Cyceron, 14000 Caen, France.**Contact information:**

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Abstract (238 words)

Significance: Redox pioneer Helmut Sies attempted to explain reactive species' challenges faced by organelles, cells, tissues, and organs *via* three complementary definitions: (1) oxidative stress, i.e. the disturbance in the prooxidant-antioxidant defense balance in favor of the prooxidants, (2) oxidative eustress, the low physiological exposure to prooxidants, and (3) oxidative distress, the supraphysiological exposure to prooxidants.

Recent Advances: Identification, concentration and interactions are the most important elements to improve our understanding of reactive species in physiology and pathology. In this context, the reactive species interactome (RSI) is a new multilevel redox regulatory system that identifies reactive species families, reactive oxygen species (ROS), reactive nitrogen species (RNS), and reactive sulfur species (RSS), and integrates their interactions with their downstream biological targets.

Critical Issues: We propose a united view to fully combine reactive species identification, oxidative eustress and distress, and the RSI system. In this view, we also propose including the forgotten reactive carbonyl species (RCS), an increasingly rediscovered reactive species family related to the other reactive families, and key enzymes within the RSI. We focus on brain physiology and pathology to demonstrate why this united view should be considered.

Future Directions: More studies are needed for an improved understanding of the contributions of reactive species through their identification, concentration, and interactions, including in the brain. Appreciating the reactive species interactome in its entirety should unveil new molecular players and mechanisms in physiology and pathology in the brain and elsewhere.

“Remember to look up at the stars and not down at your feet. Try to make sense of what you see and wonder about what makes the universe exist. Be curious. And however difficult life may seem, there is always something you can do and succeed at. It matters that you don't just give up.” Stephen William Hawking

Introduction

“Stress is the spice of life” is a famous quote by Hans Selye (210), who, in 1925, originally, defined stress as a general adaptation syndrome with three stages: alarm reaction, resistance, and exhaustion (208–210). Subsequently, redox pioneer Helmut Sies helped the concept of stress evolve, especially regarding the prooxidant-antioxidant balance and the concentration-dependent functions of stress molecules. After proving the prooxidant reactive oxygen species (ROS) hydrogen peroxide (H₂O₂) is normally produced in intact eukaryotic cells by studying the steady-state level of the antioxidant defense enzyme catalase, Sies defined oxidative stress in 1985 as “a disturbance in the prooxidant-antioxidant balance in favor of the former” (114, 216, 219, 221). This definition was updated in 2007 as “an imbalance between prooxidants and antioxidants in favor of the prooxidants, leading to a disruption of redox signaling and control and/or molecular damage” (222). In 2015, Sies legitimately argued for clearly naming the individual prooxidants instead of applying only the generic labels of oxidative stress and ROS (217). Finally, in 2017, Sies defined oxidative eustress as “low physiological exposure to prooxidants” with specific targets involved in redox signaling, and oxidative distress as “supraphysiological exposure to prooxidants” with unspecific targets, disrupted redox signaling and damaging molecule modifications (218, 220).

From physiology to pathology, likely related to tissue-specific metabolome, excessive stress is indeed a major risk factor in the lungs, liver, kidneys, heart, and brain, the metabolically active organs vital for survival (46, 122, 142, 238). In humans, the brain represents approximately 2% of total body weight but consumes 20% of total basal body oxygen and 20% of the body's energy. It is one of the most metabolically active of all organs (52, 196). Importantly, the brain is also highly susceptible to oxidative stress, specifically oxidative distress, for several reasons (52). One of these is due to the multifaceted roles of reactive species themselves, especially superoxide anion (O₂^{•-}) and

hydrogen peroxide (H_2O_2), in redox signaling (52). Another source of oxidative distress is hydrogen peroxide generated by the metabolism of neurotransmitter dopamine *via* monoamine oxidases (MAO) and by oxidative phosphorylation (OXPHOS) in mitochondria (52). Low endogenous antioxidant defense in the brain relative to other organs, especially low catalase and glutathione (GSH) content, makes the brain susceptible to oxidative distress (52). Mitochondria, including those in neurons and microglia, the resident immune cells in the brain, perform oxygen-dependent OXPHOS for O_2^- and bioenergetic metabolite ATP generation, contributing to oxidative distress (52). They have roles in many processes such as cell death and calcium homeostasis involved in synaptic plasticity (52). Neuronal activity and death also occur when the brain is enriched in redox-active transition metals ferrous iron (Fe^{2+}) and cuprous ion (Cu^+) relative to other organs (52). Furthermore, enriched unsaturated lipids including omega-3 docosahexaenoic acid in the brain cause distress due to their susceptibility to lipid peroxidation related to cell death including ferroptosis (52). Finally, brain susceptibility is region- and time-dependent, depending on the condition that induces oxidative distress and the endogenous antioxidant capacity (104, 121, 248). The following four areas of the brain are most susceptible to oxidative stress: the cerebral cortex, the largest site of neural integration involved in many functions including motor function, language processing and planning; the hippocampus, the dedicated region for neurogenesis during adulthood with its major role in learning and memory; the striatum that coordinates cognition including decision-making, action planning, and motivation; the cerebellum that coordinates motor movements (104, 121, 248).

This review focuses on reactive species identification, concentration, and interactions, including those through the brain's key enzymes. We urge the scientific community to consider together ROS, reactive nitrogen species (RNS), reactive sulfur species (RSS), and likely the forgotten reactive carbonyl species (RCS) to improve our understanding of oxidative eustress and distress in physiology and pathology.

Identification, concentration, and interactions of the reactive species

We propose here a united view to (1) name the reactive species, i.e. identification, (2) consider the concentration-dependent functions of the different reactive species, i.e.

concentration, and finally (3) integrate the different reactive species in a dynamic interactome, i.e. interactions. In 2017, this dynamic interactome was named the reactive species interactome or RSI, a multilevel integrative concept underappreciated in physiology and pathology (53). The RSI is defined as the interactions between reactive species and downstream biological targets, prevalently cysteine thiols in proteins, the so-called redox switches, and also many other elements including lipids and DNA (20, 53). RSI-related structural and functional modifications of antioxidant defense enzymes, transcription factors, molecule transporters, phosphatases, kinases, and other proteins will change adaptations from short-term to long-term and even induce alterations (20, 53). Therefore, sensors and transducers of any changes in the intracellular and extracellular environments, including those related to bioenergetic metabolism, redox signaling, and nutritional status, should be considered reactive species (20, 53). The RSI is still poorly supported by original publications, and there is massive research potential in studying the interactome. We consider the strategy focusing on identification, concentration through oxidative eustress and distress, and interactions through the RSI regarding how stress should be considered in physiology and pathology (**Fig.1**).

Endogenous key sources and interactions of ROS, RNS, RSS, and RCS

Considering the sources of the main endogenous reactive species, including intra- and inter-species interactions and those with their downstream targets, will improve understanding of oxidative stress phenomena. In a non-exhaustive manner, we overview key sources and interactions of ROS, RNS, RSS, and the neglected RCS to strengthen the relationship between themselves and show that the RSI needs to integrate the RCS family and key enzymes for a thorough understanding (**Fig. 2**).

Three reactive species sources include, (1) organelles, (2) enzymes, and (3) chemical reactions between reactive species and with transition metal ions. To elaborate key connections between the reactive species families, including those with key enzymes, we summarize ROS, RNS, RSS, and RCS metabolism.

Reactive oxygen species metabolism

ROS initiates the generation of O₂-derived reactive species using the precursor O₂ to form O₂⁻, then H₂O₂, hydroxyl radicals OH[·], OH⁻ and many other derivative species (20, 53, 223, 225) (**Fig. 2**). As in the metabolism of other reactive species families, ROS metabolism is regulated by enzyme activities and chemical reactions tightly linked to organelle functions. Mitochondria, peroxisome, the endoplasmic reticulum (ER), and lysosome are key organelles in this regard (20, 53, 64, 223, 225). From O₂, O₂⁻ is mainly generated by (1) OXPHOS complexes I, and III and other proteins such as glycerol 3-phosphate dehydrogenase and 2-oxoglutarate dehydrogenase in mitochondria, (2) fatty acid β -oxidation, iron-sulfur flavin hydroxylase xanthine oxidoreductase (XOR) and urate oxidase (UO) in the peroxisomal matrix, and electron transport chain in the peroxisomal membrane, and (3) nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, including NOXs and dual oxidases, and the microsomal monooxygenase system (MMO) which contains cytochrome P450 oxidase in the ER (225). In addition, nonheme iron-containing dioxygenases lipoxygenases and cyclooxygenases also generate O₂⁻ from polyunsaturated fatty acids (PUFAs) (225). Then, O₂⁻ reduces key transition metal ions iron Fe³⁺, copper Cu²⁺, and manganese Mn³⁺, which generates O₂ (101, 225, 247). Importantly, O₂⁻ is also metabolized to generate H₂O₂, one of the most stable ROS (20, 53, 223, 225). Without developing all H₂O₂ sources, including spontaneous dismutation of O₂⁻, polyamine catabolism with copper-containing diamine oxidase and thymidine catabolism, mitochondrial MAO, copper-dependent lysyl oxidases, peroxisomal enzymes such as XOR, UO and acyl-CoA oxidases, and the ER oxidoreductin-1 related to glutathione metabolism GSH/GSSG and MMO system, it is important to highlight that one of the major antioxidant enzymes catalyzes the reduction of O₂⁻ to H₂O₂, superoxide dismutase (SOD) (53, 78, 100, 223, 225).

Hydrogen peroxide is then metabolized to generate other ROS, O₂, and H₂O, and regulate transition metal ion reactivities (53, 100, 223, 225). Among several enzymes, glutathione peroxidases (GPXs) through GSH/GSSG metabolism, and peroxiredoxin (PRDX) generate H₂O from H₂O₂ (181, 225). Two vital enzymes also must be highlighted, the important antioxidant defense enzyme catalase and the heme enzyme myeloperoxidase (MPO). Catalase, the most abundant peroxisomal antioxidant enzyme, dismutates H₂O₂ to O₂ and

H₂O (53, 100, 168, 174, 221). Myeloperoxidase catalyzes the oxidation of Cl⁻ by H₂O₂ to hypochlorous acid (HOCl) (83, 178). In addition, H₂O₂ reacts with transition metal ions Fe²⁺ or Cu⁺ to generate OH[·], OH⁻ and corresponding reactive Fe³⁺ or Cu²⁺ in the Fenton reaction (118, 225). The Fenton reaction with Fe²⁺ occurs mainly in the lysosome, an essential acidic organelle for cellular degradation and recycling of proteins, DNA, RNA, lipids and carbohydrates (64). This lysosomal reaction induces lysosomal stress, leakage, and multiple intracellular dysfunctions including bioenergetic metabolism and autophagy alterations (64). Through another reaction, the Haber-Weiss reaction, H₂O₂ also reacts with O₂⁻ to generate OH[·], OH⁻ and O₂ (118, 225). Finally, multiple antioxidant defense systems such as glutaredoxin, OXPHOS complex IV cytochrome c oxidase, glutathione (GSH/GSSG), and vitamins contribute to regulating the entire ROS metabolism (53, 223, 225). This partial view of ROS metabolism will be completed later with regard to SODs, catalase, XOR, and MPO as the four key enzymes.

Reactive nitrogen species metabolism

Closely related to iron homeostasis, RNS metabolism is the generation of nitric oxide (NO)-derived reactive species mainly from L-arginine and NO synthase (NOS) activities (20, 53, 74, 76, 120, 140) (**Fig. 2**). From L-arginine, O₂ and cofactors tetrahydrobiopterin (BH₄), NADPH, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), NO is generated by three isoforms of NOS, neuronal NOS (nNOS, NOS I), constitutively expressed in the central nervous system (CNS), inducible NOS (iNOS, NOS II) that is expressed in many cell types including macrophages and dendritic cells, and endothelial NOS (eNOS, NOS III) mainly expressed in endothelial cells (74, 76, 120, 225). While nNOS and eNOS are calcium-dependent enzymes, iNOS is calcium-independent (74, 76).

Using O₂, oxidation of L-arginine by coupled NOS with cofactors including NADPH generates NO, NADP and L-citrulline, which is also an L-arginine precursor through the citrulline-NO cycle (12, 74, 76, 120). Nitric oxide then reacts with O₂ to generate nitrogen dioxide (NO₂) and with NO₂ to form dinitrogen trioxide, which reacts with water to produce nitrite (NO₂⁻) or dissociates to form NO and NO₂ (74, 76, 120). Nitrite oxidation with O₂ leads to the generation of nitrate (NO₃⁻) (74, 76, 120). Nitric oxide is also generated by the following process: nitrate reductase (NR) catalyzes the reduction of nitrate into

nitrite, and nitrite reductase (NiR) reduces nitrite into NO (120). The RNS metabolism also includes other reactive species such as nitroxyl, nitrous acid, hydroxylamine, and ammonia that are not discussed here (120). This partial view of RNS metabolism will be completed later regarding NO as the key reactive species and NOS as the key enzyme.

Reactive sulfur species metabolism

Reactive sulfur species are derived from hydrogen sulfide (H₂S) (20, 29, 53, 128, 171, 272) (**Fig. 2**). From essential amino acid L-methionine recycling and transsulfuration pathway with L-homocysteine and L-cysteine, the RSS-related enzymes cysteine-β-synthase (CBS), cysteine-γ-lyase (CSE here, a.k.a. CGL), cysteine aminotransferase (CAT) and 3-mercaptosulfotransferase (3-MST) are the key enzymes involved in H₂S production (29, 53, 128, 157, 171, 172, 233, 272). First, L-methionine catabolism leads to L-homocysteine biosynthesis (29, 128, 171, 171, 233, 272). Cysteine-γ-lyase then converts L-homocysteine to L-homolanthionine and H₂S (29, 128, 171, 171, 233, 272). The CBS and CSE enzymes convert L-homocysteine and L-cysteine to L-cystathionine and H₂S, and L-cystathionine is further converted to L-cysteine by CSE (29, 128, 171, 171, 233, 272). In addition, L-cysteine is metabolized either by CBS to produce H₂S, L-serine and L-lanthionine, by CSE to generate H₂S, ammonium and pyruvate, or by CAT to 3-mercaptopyruvate (29, 128, 157, 171, 171, 233, 272). The enzyme CAT is also both an aspartate aminotransferase (AST) and a glutamate oxaloacetate transaminase (GOT) that generates α-ketoglutarate and aspartate from oxaloacetate and glutamate in mitochondria (GOT2) catalyzes the reverse reaction in the cytosol (GOT1) (155, 157). Cystine, the dimeric form of L-cysteine, is converted by CSE to L-thiocysteine, producing H₂S through thiol (RSH)-dependent reactions (171, 233). The 3-mercaptopyruvate which is also produced by conversion of D-cysteine by D-amino acid oxidase (DAO) and that spontaneously generates H₂S, is the substrate of 3-MST to generate pyruvate, and finally, bound sulfane sulfur (171, 233). This sulfur generation results in the release of H₂S through the thioredoxin (TRX) enzyme and dihydrolipoic acid (DHLA) (171, 233). This pathway is standard for H₂S generation, although TRX and DHLA are part of the unconventional pathway (171). In this pathway, H₂S is generated from thiosulfate (S₂O₃²⁻) through reductant DHLA or thiosulfate reductase coupled to GSH oxidation or 3-MST (171). Associated with GSH/GSSG and NADPH/NADH systems, non-enzymatic reactions through

thiocysteine persulfides and polysulfides also generate H₂S (29). Moreover, mitochondrial OXPHOS complex I is a source of H₂S due to its accessory sulfurtransferase subunit (171). Finally, not discussed here, volatile organic sulfides such as carbon disulfide, carbonyl sulfide and sulfur dioxide, and acid-labile sulfide in iron centers, including cytochromes and aminothiols such as cysteinylglycine are unconventional sources of H₂S (171).

Once H₂S is produced, as its accumulation is toxic, H₂S catabolism occurs by oxidation to form thiosulfate (29, 128, 171). This reaction also occurs in mitochondria, where sulfide quinone oxidoreductase oxidizes H₂S to produce persulfide (29, 128, 171). Sulfite and sulfate are also derived from H₂S and related to thiosulfate (29, 128, 171). Thiosulfate is converted into sulfite through thiosulfate sulfurtransferase or rhodanese then into sulfate, and sulfite contributes to H₂S generation (29, 128, 171). Hydrogen sulfide catabolism also occurs by methylation to produce methanethiol, then dimethylsulfide by thiol S-methyltransferase (29). Finally, H₂S is oxidized into hydrogen thioperoxide, sulfinic acid then sulfonic acid (128). Although many reactive sulfur species are compelling, we will not discuss all the species and pathways. Two species we will discuss are polysulfides (H₂S_n), including persulfides (H₂S₂). These species are of increasing research interest, and their production and catabolism conventional and unconventional pathways (171). Finally, polysulfides are unstable and their catabolism tend to generate H₂S (171). This partial view of RSS metabolism will be completed later, considering H₂S as the notable reactive species.

Reactive carbonyl species metabolism

The sprawling network of the electrophilic, highly reactive, often forgotten RCS family is partially illustrated (**Fig. 2**). The key RCS members worthy of investigation include glyoxal (GO), acrolein, glucosone, acetaldehyde, glyceraldehyde-3-phosphate (G3P), and the three most abundant malondialdehydes (MDA), methyglyoxal (MGO)s and 4-hydroxy-trans-2-nonenal (4-HNE) (211). The most abundant RCS are derived from PUFA peroxidation into lipid hydroxyperoxides through non-enzymatic reactions (4, 8, 187, 211). Fortunately, PUFA peroxidation is reversible due to notable enzymes GPX and PRDX (94, 211). The RCS are also produced by other nonenzymatic reactions such as oxidative modifications of

amino acids (including threonine) and glycation of proteins through reduction of carbohydrates (including glucose) (158, 211).

Notably, RCS, including MGO, are generated as metabolic intermediates during glycolysis and polyol processing (205, 211). Methylglyoxal is mainly generated during glycolysis through nonenzymatic catabolism of triose phosphates G3P, dihydroxyacetone-phosphate (DHAP) and the glycation pathway to ultimately produce advanced glycation end products (AGEs)(205, 211). The AGEs and lipoxidation end products (ALEs), also induced by RCS are irreversible toxic products (205, 211). The end-product fructose from the polyol glucose-sorbitol-fructose pathway, is also a precursor of MGO through triose phosphate formation (205, 211). Finally, MGO is generated by ketone body catabolism, including oxidation of acetone (205, 211). Fortunately, the glyoxalase defense system counteracts the accumulation of MGO by converting MGO into D-lactate (205, 211).

Long seen as side products from ROS following lipid peroxidation, careful examination of RCS shows that this family strengthens the connections between ROS, RNS, and RSS families in such a way that the RCS family could be the missing piece of the “stress puzzle” that will change perspectives and contribute to revealing new pathways. This partial view of RCS metabolism has presented the notable reactive species MDA, MGO, and 4-HNE and the key enzymes, GPX as well PRDX.

The metabolism and interactome of notable reactive species and key enzymes

Connections between the notable reactive species, families (including multiple ROS, NO, H₂S, and MDA, MGO, and 4-HNE) and key enzymes (SOD, catalase, XOR, MPO, NOS, GPX, and PRDX) reinforce the united concept of RSI highlighted in our overview (**Fig. 2**).

In a recent demonstration of this connectedness, Kenneth Olson and colleagues showed in a concentration- and oxygen-dependent manner that SODs oxidize H₂S into polysulfides, including persulfide H₂S₂, and to a lesser extent H₂S₃ and H₂S₅, which may be an ancient mechanism to detoxify or manage RSS (173). Thus, both ROS and RSS metabolism are regulated by SODs. Moreover, in a pH-dependent manner, catalase is also involved in RNS metabolism: in the presence of H₂O₂, catalase oxidizes sodium azide (NaN₃), an inhibitor of mitochondrial cytochrome c oxidase in OXPHOS complex IV and catalase, into at least RNS NO₂⁻ (nitrite) and NO₃⁻ (nitrate) (168). In addition, the Olson research group recently

proposed that catalase is also a sulfide-sulfur oxido-reductase during normoxia and hypoxia, as a sulfide oxidase by metabolizing H₂S under the influence of H₂O₂, as a sulfide reductase generating H₂S from dithiothreitol (DTT), and by eliminating polysulfides H₂S_n in a concentration- and oxygen-dependent manner (174). Thus, ROS, RNS, and RSS metabolism are altogether regulated by catalase. The enzyme XOR is found in peroxisomes, where, in addition to generating O₂⁻, catalyzes the reduction of nitrite and nitrate into NO, thus regulating ROS and RNS metabolism (225). The MPO enzyme is also a major NO scavenger that up-regulates iNOS activity by reducing feedback inhibition of NO, and oxidizing nitrite to form nitrogen dioxide or peroxynitrite (ONOO⁻), the so-called MPO-H₂O₂-nitrite system (23, 79). It has also been proposed recently that MPO is a key regulator of RSS metabolism by oxidizing H₂S with H₂O₂ or O₂ in the absence of H₂O₂ (83, 178). Furthermore, the MPO-H₂O₂-chloride system generates from hydroxy-amino acids several RCS such as aldehyde, acetone, and acrolein (211). Thus, ROS, RNS, RSS, and RCS metabolism are regulated by MPO.

Nitric oxide reacts with O₂⁻ to form peroxynitrite (ONOO⁻), and H₂S to form nitroxyl, thus linking ROS, RNS, and RSS metabolism (171, 225, 258). Importantly, NOS activity directly links ROS and RNS, and indirectly RSS through NO (76, 197, 225, 258). Indeed, while coupled NOS with cofactors leads to NO generation, uncoupled NOS produces O₂⁻, thus fueling O₂⁻-related reactive species including the peroxynitrite positive feedback loop, and reduces NO bioavailability, thus impacting NO reactive species targets such as H₂S (76, 197, 225, 258). Together, NO and NOS regulate at least ROS, RNS, and RSS metabolism.

Hydrogen sulfide sits at the crossroads of ROS, RNS, RSS, and RCS metabolism: it reacts with O₂ in the presence of transition metal ion Fe³⁺ to form sulfur dioxide and water, with O₂⁻ to form hydroperoxyl, with oxidized metal center proteins, mostly hemes including iron-heme cytochromes, to form O₂⁻, with HOCl to form polysulfides, and with ONOO⁻ to form thionitrite and OH⁻ (109, 164, 171, 258). Hydrogen sulfide can efficiently scavenge at least the aldehyde 4-HNE at physiological concentrations, meaning oxidative eustress in neuronal cells, protecting cells against MGO-induced damage in keratinocytes, and increasing MDA levels in rat cerebral cortex (31, 206, 266).

Finally, to complete these examples, the notable species and enzymes in RCS metabolism, i.e. MGO, MDA, 4-HNE, GPX, and PRDX, link together ROS, RNS, RSS, and RCS metabolism.

Hydrogen peroxide oxidizes the MGO and aldehydes, including MDA and 4-HNE, to form carboxylic acids (165, 201). Moreover the RCS are oxidized by H_2O_2 and $ONOO^-$ to form adducts and intermediate products, ultimately forming acetate, formate, and methyl radicals (165, 201). In addition, MDA and 4-HNE inhibit XOR activity through direct interactions with XOR oxidase and dehydrogenase forms, while a GSH increase blocks this inhibitory effect (48). The highly reactive dicarbonyl MGO inactivates GPX enzymes by direct interactions with the glutathione binding site (185). Importantly, GPX and PRDX enzymes regulate one of the most important sources of RCS, lipid hydroperoxides (9, 16, 137, 161, 195, 269). Specifically, the selenoenzyme GPX4 and PRDX, including PRDX4, which are sensors and regulators of peroxides, neutralize lipid hydroperoxides (9, 16, 137, 161, 195, 269).

Due to its direct reactions with ROS, RNS, and RSS and key enzymes, the RCS family should be considered as important as ROS, RNS, and RSS families in the reactive species interactome.

Notable reactive species, key enzymes, and the reactive species interactome in the brain

As developed in the introduction, we are focused on the brain, which, of all organs, is one of the most metabolically active and sensitive to oxidative distress. From physiology to pathology, from oxidative eustress to distress, considering 1) our strategy of identification-concentration-interactions, 2) the notable reactive species and key enzymes, and 3) descriptions of individual and puzzling implications of ROS, RNS, RSS, and RCS, we combined key findings to reveal the RSI (including RCS) potential in the brain. We concentrate the brain physiology discussion on adult neurogenesis, cell death and aging, and regard the brain pathology on depression, ischemia, neurodegenerative disorders, and cancers.

Physiology: the brain adult neurogenesis

In mammals, throughout life, neurogenesis, which occurs in several brain regions such as the hippocampal dentate gyrus and lateral ventricles, is defined as “the formation of new neurons from neural stem cells (NSC) and progenitor cells” (19, 146). The existence of adult neurogenesis, one that occurs in adulthood has been intensively debated due to

discrepancies between different studies using histology and multiple biomarkers (19, 146). Historically, in 1998, adult neurogenesis was observed continuously, at least in the human hippocampus (70). Then, after lengthy debates, in 2019, persistent adult neurogenesis in the hippocampal dentate gyrus was confirmed in healthy adult humans up to 90 years-old, (146, 159). As solid evidence is growing in support of human adult neurogenesis (in the hippocampus and elsewhere), the field has moved towards reconciliation of various neurogenesis biomarkers and open questions on the molecular mechanisms regulating neurogenesis including through oxidative stress (146, 159, 275).

The RSI in brain adult neurogenesis

The neurogenesis field is currently investigating more than twenty different biomarkers (146, 275). An increasing number of studies highlight the involvement of several reactive species in brain adult neurogenesis, although the molecular mechanisms between reactive species and neurogenesis biomarkers require further investigation (**Fig. 3**). First, differentiation during adult neurogenesis induces oxidized glutathione accumulation and at least mitochondrial O_2^- overgeneration (251). Transient oxidative distress due to overgeneration of mitochondrial O_2^- promotes NSC and progenitor cell differentiation and, therefore, adult neurogenesis (251). High levels of H_2O_2 are then required for regular NSC and progenitor cells self-renewal, a process related to DCX, Nestin, and FOXO proteins (130). For example, the self-renewal process is modulated by the tumor suppressor and metabolic regulator PTEN protein (Phosphatase and tensin Homolog), which regulates DCX and Nestin expression, and which is a negative regulator of phosphoinositide 3-kinase (PI3K)-AKT-mTORC1 pathway (130). The PTEN protein inactivation through overoxidation due to H_2O_2 promotes NSC and progenitor cells self-renewal (130). Moreover, inhibition of H_2O_2 overgeneration counteracts NSC proliferation (97). Oxidative distress due to H_2O_2 activates adult neurogenesis. Interestingly, from the antioxidant defense side, SOD deficiency induces a reduction in adult neurogenesis at all stages, from self-renewal to differentiation related to DCX, NeuroD and GFAP biomarkers (107). In addition, NSC and progenitor cell proliferation are increased by the accumulation of catalase in mitochondria (138). Finally, MPO inhibition increases adult neurogenesis through at least DCX and Sox2

stimulation (271). Superoxide dismutase, catalase and MPO are key enzymes to investigate in adult neurogenesis.

Increasing the complexity, NO generated by neuronal NOS is a negative regulator of NSC and progenitor cell proliferation in healthy brain while its overgeneration after brain damage promotes proliferation and then adult neurogenesis (72, 160, 177). The PTEN and AKT proteins are inactivated by nitrosylation mediated by NO (188). While NO has a dual role in adult neurogenesis, transient ONOO⁻ accumulation promotes NSC and progenitor cell self-renewal, proliferation, and even differentiation through activating the hypoxia-inducible factor 1-alpha (HIF-1A) signaling pathway (43). Transient oxidative distress due to ONOO⁻ activates adult neurogenesis. Finally, the H₂S promotes NSC and progenitor cell proliferation and differentiation in association with increased phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) to activate the kinase activity and downstream targets (141, 245). All this evidence indicates, that transient oxidative distress mediated by ROS, RNS, and RSS metabolism activates adult neurogenesis.

However, this is not the case for RCS metabolism. The accumulation of MDA due to lipid peroxidation inhibits NSC and progenitor cell proliferation, and MGO impairs neurogenesis by inducing cell death of NSC (47, 183). Therefore, oxidative distress mediated by RCS inhibits adult neurogenesis. Moreover, regarding key enzymes GPX and PRDX, the situation is even more complicated. While GPX1 does not regulate adult neurogenesis, other GPXs such as GPX4 increase adult neurogenesis (191, 244, 269). The same for PRDXs as PRDX1, PRDX2, and PRDX4 stimulate adult neurogenesis while PRDX6 inhibits adult neurogenesis (268).

In adult neurogenesis, considering interactions between the four reactive species metabolism including through key enzymes, the RSI is fully committed and reveals all its potential when integrated with RCS metabolism (**Fig. 2**).

The RSI in brain cell death

Brain vulnerability increases due to neuroinflammation and decreases in neuroplasticity, dysregulation of neuronal activities, and alteration of bioenergetic metabolism (153). Brain vulnerability is also exacerbated by increased intracellular oxidation, damage, and cell death in neurons, astrocytes, oligodendrocytes and microglial cells, at the intersection of

brain physiology and disorders (153). Cell death is an inevitable consequence of cell life, and there are at least twelve types of cell death (80) (**Fig.4**). In the brain, apoptosis, necrosis including necroptosis, oxytosis, and ferroptosis (two names of the same pathway or two highly similar pathways), autophagy-dependent cell death, and parthanatos poly ADP-ribose polymerase 1-dependent cell death are the main cell death types which are all initiated by bioenergetic metabolism dysregulation and oxidative distress (34, 135, 170).

First, in the brain, mitochondrial O_2^- is a major regulator of necroptosis by oxidizing the key necroptosis factor receptor-interacting protein kinase 1 (RIP1) and activating the necrosome (59). This regulation is exacerbated by hyperglycemia that induces a shift from apoptosis to necroptosis through mitochondrial O_2^- which both oxidizes necroptosis RIP1 and inactivates apoptosis factors caspases-3/6/7 (59). In other words, oxidative distress mediated by ROS O_2^- triggers necroptosis and inhibits apoptosis. In addition, in the brain, H_2O_2 accumulation initiates the main cell death types, including ferroptosis, the newly discovered non-apoptotic cell death-type characterized by accumulation of H_2O_2 as well as cytosolic adenosine triphosphate (ATP) depletion, active iron Fe^{2+} accumulation, antioxidant GSH depletion, GPX4 inactivation, and ultimately, by the deadly increase in lipid peroxidation, the most important source of RCS (34, 63, 135, 170). The excitatory neurotransmitter glutamate induces ferroptosis at high concentrations in the brain, positioning ferroptosis as an emerging major cell death nexus linking iron metabolism, lipid metabolism, bioenergetic metabolism, antioxidant, and reactive species metabolism associated with glutamate toxicity (150, 229). Moreover, key enzyme SOD regulates apoptosis as an increase in SOD1 activity delays or even prevents apoptosis in neurons (92). Interestingly, the role of SOD1 in apoptosis is tightly linked to NO as NO mediates apoptosis, and NO-SOD balance has been shown as a key determinant in apoptosis initiation (49). An increase in key enzyme catalase also prevents apoptosis by metabolizing H_2O_2 and ultimately regulating apoptosis factors, including Bax and Bcl-2 in neurons (69, 224). Key enzyme XOR also regulates both apoptosis and necroptosis through O_2^- overgeneration (18). Finally, enzyme MPO regulates apoptosis and ferroptosis through H_2O_2 and HOCl modulation, and MPO inhibition reduces apoptosis and ferroptosis in the brain (37, 213). The key enzymes SOD, catalase, XOR, and MPO merit further investigation in studying brain cell death.

Oxidative distress mediated by the RNS family also stimulates the main cell death-types in the brain. Accumulation of NO induces apoptosis through the nitrosylation of key proteins involved in apoptosis signaling, including caspases 3/8/9 and B-cell lymphoma 2 (Bcl-2), and accumulation of ONOO⁻ activates apoptosis, necroptosis, parthanatos, and autophagy-dependent cell death in neurons, including through tyrosine nitration of heat shock protein 90 (Hsp90), α -synuclein, cytochrome c, and through DNA damage (188, 192). In contrast to RNS, oxidative distress mediated by H₂S and sulfite is neuroprotective by inhibiting apoptosis and oxytosis. Anti-inflammatory and anti-apoptotic, H₂S physiologically and pharmacologically reduces cell-death type activation, including after a brain injury, even though very high levels of H₂S can disrupt mitochondrial function and trigger at least apoptosis in neurons (99, 274). Sulfite also protects neurons against oxytosis, a cell death-type due to H₂O₂ accumulation, GSH depletion, lipoxygenase activation, and calcium influx (124, 135).

Finally, oxidative distress mediated by RCS is also a major cell death-types regulator to consider, at least in the brain. The MGO triggers apoptosis in neurons (55, 61, 86). Furthermore high levels of 4-HNE and MDA due to increased lipid peroxidation lead to apoptosis, necrosis, autophagy-dependent cell death, and, most importantly, ferroptosis (55, 61, 86). Interestingly, the key enzyme GPX1 protects immature neurons against H₂O₂-mediated apoptosis, and GPX4 is crucial in controlling ferroptosis (207). Key enzyme PRDX6 protects astrocytes and microglia against ferroptosis (154, 180).

Altogether, while oxidative distress mediated by ROS, RNS, and RCS activates several brain cell death-types, i.e. apoptosis, necrosis including necroptosis, autophagy-dependent cell death, and ferroptosis, oxidative distress mediated by RSS inactivates at least apoptosis and oxytosis. Therefore, considering both the RSI in its entirety, including the RCS family and key enzymes at the intersection of the reactive species families, will reveal all RSI potential in brain cell death. This information is important in understanding roles and switching between different cell death-types in physiology, including aging and pathology (**Fig. 4**).

Is RSI the eleventh hallmark of brain aging ?

Brain aging has a signature of ten hallmarks: neuroinflammation, oxidative damage, adaptive stress response signaling alteration, bioenergetic metabolism dysregulation, mitochondrial dysfunction, aberrant neural network activity, neuronal calcium homeostasis dysregulation, stem cell exhaustion, molecular waste disposal impairment, and DNA repair impairment (153, 264)(**Fig. 5**). Multiple pathways are involved in brain aging through many different biomarkers not listed here to focus our overview on the reactive species themselves. Impaired adult neurogenesis, overactivation of cell death including apoptosis, and cellular replicative senescence are involved in brain aging (153, 264).

It is important to remember that replicative senescence is probably a key driver of aging (14, 153, 273). Replicative senescence, a powerful anticancer mechanism, is a stable cell cycle arrest associated with telomere shortening, senescence-associated beta-galactosidase (SA- β -gal) activity, kinase inhibitor proteins p16INK4 and p21 activation, and a senescence-associated secretory phenotype (SASP) including proteases, growth factors and pro-inflammatory cytokines (133, 264). Senescence is both a physiological and pathological process related to several reactive species and is implicated in aging, including that in post-mitotic neurons and oligodendrocytes, as recent evidence argues that senescence occurs in these cells (14, 133, 153).

We propose that dysregulated RSI is the 11th hallmark of brain aging that links cellular replicative senescence, cell death types, adult neurogenesis, and the ten established hallmarks (**Fig. 5**).

First, at a minimum mitochondrial O_2^- accumulation and antioxidant defense decline are the major events that trigger the ten hallmarks of brain aging (153). Oxidative distress mediated by mitochondrial O_2^- in the brain, including the frontal cortex, hippocampus, and amygdala, initiates brain aging (228). Interestingly, in mitotic astrocytes, highly glycolytic compared to other glial cells, mitochondrial O_2^- does not strongly contribute to cellular senescence while its contribution is significant in other glial cells (228). Overgeneration of H_2O_2 also leads to senescence of mitotic astrocytes with SA- β -gal activity and probable SASP, and mitotic microglial cells with telomere shortening, SA- β -gal activity and probable SASP (153, 256). Compared to astrocytes, post-mitotic neurons, which are much less

glycolytic, and so more dependent on mitochondrial function, generate substantial mitochondrial O_2^- (27, 228). Moreover, overgeneration of H_2O_2 seems to lead to senescence of human neural progenitor cells and post-mitotic neurons with SA- β -gal activity and probable SASP characteristics (153, 256, 273). All this evidence indicates oxidative distress mediated by H_2O_2 initiates brain aging. In addition, key enzymes SOD, catalase, XOR, and MPO play key roles in aging, including in the brain as brain aging is associated with progressive decline in SOD and catalase activities. The use of SOD/catalase mimetics may contribute to reversing age-related declines including in cognitive function, and as XOR and MPO activities dangerously increase with aging (50, 87, 243, 250). Antioxidant defense decline and oxidative distress mediated by ROS are clearly pro-aging, including in the brain.

Reactive nitrogen species metabolism is also actively involved in brain aging, although heterogeneously in nitrosative vulnerability depending on brain cell types (26, 27, 228). Mitotic glycolytic astrocytes are not vulnerable to NO and ONOO⁻ while post-mitotic neurons, which are more dependent on mitochondrial respiration, are vulnerable to both NO and ONOO⁻ (26, 27, 228). Nitric oxide, both an anterograde and retrograde neurotransmitter in synapses, and ONOO⁻ contribute to protein nitration, nitrosylation, and consequently brain aging (188). Aging including in brain is associated with nitrative damages, and nitrosylation of amyloid β -peptides, and proteins involved in regulation of immune response, including S100, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) (188). Oxidative distress mediated by RNS is pro-aging including in the brain.

Reactive sulfur species metabolism is also actively involved in brain aging through H_2S and H_2S_n (polysulfide), which are suggested to act as gliotransmitters (147, 149). Oxidative distress mediated by H_2S and H_2S_n supports brain function including memory formation during aging by modulating N-methyl-D-Aspartate subtype glutamate receptors (NMDARs) through sulfuration (147, 149). The NMDARs are excitatory glutamate receptors involved in neuronal plasticity, and learning and memory. They are dysregulated during brain aging and numerous brain pathologies (147, 149). In addition, H_2S also exerts anti-aging properties by inhibiting ROS and RNS generation, and by activating sirtuin 1 (SIRT1), a major anti-aging and anti-senescence NAD (nicotinamide adenine dinucleotide)-dependent

protein deacetylase found in the brain (277). Oxidative distress mediated by RSS is anti-aging, including in the brain.

Finally, oxidative distress mediated by 4-HNE and MDA is pro-aging. The 4-HNE and MDA are overgenerated by increased lipid peroxidation and accumulate in tissues and organs with age, including in the brain (115, 153). However, with no clear molecular explanation, a progressive decrease in MGO levels associated with an increase in aldolase reductase (AR) expression, which metabolizes MGO, occurs during brain aging, thus suggesting an unsolved key role of MGO in brain aging (127). Moreover, during brain aging, reduced GSH decreases while oxidized GSSG increases, and key enzymes GPXs (including GPX4 activities) as well PRDXs (including PRDX6) decline (15, 45, 71, 145, 176, 281). Interestingly, GPX4 activity plays a key role at the intersection of apoptosis and ferroptosis, an important topic in aging research, including that exploring the brain (15, 96, 270). An increase in GPXs and PRDXs expression and activity that improve detoxification of lipid hydroperoxides is a promising route of anti-aging therapy exploration to limit detrimental oxidative distress due to 4-HNE and MDA in brain aging.

Considering that antioxidant defense decline and oxidative distress mediated by ROS, RNS, and 4-HNE and MDA are pro-aging while oxidative distress mediated by RSS is anti-aging including in the brain, the entire RSI, including RCS, has to be further investigated. A dysregulated RSI could be the 11th hallmark of brain aging (**Fig. 5**).

Conclusion on the RSI in brain physiology

Through adult neurogenesis, cell death and aging in the brain, we showed that the entire RSI should be considered instead of only one reactive species family. Knowing (1) exactly which reactive species is active in, i.e. identification, and (2) the physiological or supraphysiological concentration, i.e. concentration integrating oxidative eustress and distress, will reveal all the RSI potential in physiology, including in the brain.

Reactive species family roles vary in the physiological process, and a family is not solely detrimental or beneficial. Oxidative distress mediated by ROS, RNS and RSS promotes adult neurogenesis, while mediated by RCS inhibits adult neurogenesis. Oxidative distress mediated by ROS, RNS, and RCS triggers apoptosis, necrosis, autophagy-dependent cell death and ferroptosis, while that mediated by RSS inhibits at least apoptosis and oxytosis.

Oxidative distress mediated by ROS, RNS, and RCS is pro-aging, while that mediated by RSS is anti-aging. Together, the RCS family is coordinated together with the other reactive species families, and therefore only the RSI, including RCS, is fully committed in brain physiology.

Finally, key enzymes SOD, catalase, XOR, MPO, GPXs (including GPX4), and PRDXs require further examination in light of the entire RSI, including RCS in brain physiology. In a physiological process, the global redox effect is created by the combination between (1) effects from different reactive species families in different concentrations, (2) interactions between the different families and (3) activities of the key enzymes that contribute to the RSI dynamics. This axiom is true in physiology and pathologies.

The RSI in mental disorder depression

Oxidative stress, or better, oxidative distress, plays a significant role in mental disorders from addiction to anxiety, depression, bipolar disorder, post-traumatic stress disorder, dementia, and schizophrenia affecting almost 1 billion people worldwide (38, 240). Depression affects 300 million people worldwide, thus being the leading mental disorder, and by 2030, depression is predicted to be the second leading cause of illness worldwide, following human immunodeficiency virus infection/acquired immunodeficiency syndrome and followed by ischemic heart disease (102, 152).

Different complementary approaches such as transcriptomic, proteomic, metabolomic, and epigenetic, depression, including major depression, have been progressively better characterized to improve treatments, although complex molecular mechanisms are involved (230). More than fifteen biomarkers are predictive of this mental disorder, including a reduction in gray matter volume, overgeneration of the stress hormone cortisol, dopamine and noradrenaline reduction, glutamate accumulation, neuroinflammation, tryptophan metabolism alterations, brain-derived neurotrophic factor (BDNF), and vascular endothelial growth factor (VEGF) reduction, and possibly genetic polymorphisms (230) (**Fig. 6**). The antioxidant defense and reactive species and related targets are also increasingly considered biomarkers for depression, although the molecular mechanisms are still missing (230).

The entire RSI, including RCS, should be considered in the study of mental disorders, including depressive disorder, to improve the understanding of the targets and the molecular mechanisms (**Fig. 6**). First, an imbalance between O_2^- and H_2O_2 due to specific SOD2 genetic polymorphisms increases the risk of depression (54). Overgeneration of ROS, antioxidant defense alterations including SOD dysfunction, and decrease in GSH levels are involved in major depressive disorder through harmful overoxidation of proteins, lipids and DNA (143, 199, 249). Specific genetic polymorphisms of catalase are also associated with an increased risk of depression (199). A decrease in SOD and catalase activities and increased XOR levels are often found in depressed patients compared to healthy individuals (249). The XOR activity also increases in recurrent depressive episodes in many brain regions, including the hippocampus and thalamus (156). In addition, the accumulation of MPO enzyme in serum is a biomarker of immune dysregulation associated with major depressive disorder (246). Altogether, an imbalance between ROS, oxidative distress mediated by ROS and altered SOD, catalase, XOR, and MPO enzymes exert a pro-depressant effect.

Interestingly, it is now known that anti-depressant drugs modulate ROS/RNS generation and antioxidant defense (199, 249). Reactive nitrogen metabolism is involved in depression including major depressive disorder. In depression, neuronal NOS enzyme accumulates in several brain regions, including the hippocampus, cortex, and hypothalamus (279). Researchers have proposed that the interaction between nNOS and serotonergic signaling, and the link between nNOS and adult neurogenesis are the key deregulated mechanisms in depression (279). Inhibition of nNOS with NG-nitro-L-arginine methyl ester exhibits antidepressant properties, and several weeks of antidepressant treatment reduces NO levels in depressed patients (199, 249, 279). Thus, related to nNOS accumulation, oxidative distress mediated by RNS exerts a pro-depressant effect.

Importantly, by increasing synaptic neurotransmission and synaptic plasticity, the H_2S has an antidepressant-like effect (41). This effect is through induction of adiponectin expression, a hormone involved in glucose and lipid metabolism, that ultimately reduces autophagy and favors synapse formation in the brain, including in the hippocampus (241). Oxidative distress mediated by RSS exerts an anti-depressant effect.

Finally, an increase in lipid peroxidation, the main source of RCS, is associated with depression. Treatment with n-3PUFAs, including docosahexaenoic acid, appears as effective as antidepressant therapy by inhibiting neuronal apoptosis and reducing neuroinflammation (249). The MGO, MDA, and 4-HNE that accumulate in depressed patients are considered biomarkers of depressive disorder, and anti-depressant therapy effectively reduces their levels (62, 143, 198, 249). Oxidative distress mediated by RCS exerts a pro-depressant effect. In several studies, a decrease in key enzyme GPX activity was found in depressed patients compared to healthy individuals, while in other studies, no difference was detected (143, 249). Finally, associated with decreased BDNF growth factor in serum, the key enzyme PRDX1 accumulates in depressed patients (276).

Oxidative distress mediated by ROS, RNS, and RCS exerts a pro-depressant effect, while oxidative distress mediated by RSS exerts an anti-depressant effect. The entire RSI, including RCS, plays a clear role in depression (**Fig. 6**).

The RSI in brain ischemia

When a blood clot blocks or plugs an artery or vein in the brain, an arterial or venous occlusion, this is an ischemic stroke that occurs, creating a medical emergency for which brain aging is the highest non-modifiable risk factor (28, 65, 113, 153, 202). Every year, stroke, which includes hemorrhagic stroke (20% of the cases) and ischemic stroke (80% of the cases) accounts for approximately 80.1 million cases worldwide and 5.5 million deaths (28, 65, 113, 202). Following a stroke, *per hour*, 120 million neurons die, 830 billion synapses and 714 km/447 miles of myelinated fibers are lost, so the brain is losing nearly 3.6 years of normal aging (202). To treat arterial or venous occlusion, rapid reperfusion with thrombolysis and endovascular thrombectomy is the main therapy, and while it provides benefits, it also presents adverse effects regarding oxidative distress (28). Ischemic stroke provokes rapid oxygen and glucose deprivation, inducing excitotoxicity due to glutamate release, mitochondrial dysfunction, oxidative distress, lipid peroxidation, DNA damage, neuroinflammation and neuronal cell death through at least apoptosis and necrosis, including necroptosis (57, 153) (**Fig.7**). Oxygen deprivation followed by reoxygenation induces an increase in the blood-brain barrier (BBB) permeability partially through activation of the hypoxia-inducible transcriptional factor HIF-1 and an increase in

expression of its target genes such as matrix metalloproteinase 2 and VEGF (171, 208). Oxygen deprivation, resulting in tissue hypoxia, induces oxidative distress due to, a minimum, mitochondrial respiration deterioration and loss (91, 153). Then, rapid oxygen supply, i.e. reoxygenation due to reperfusion, exacerbates oxidative distress due to, minimally, mitochondrial respiration (57, 91, 153).

First, during ischemia/reperfusion (I/R), mitochondrial O_2^- overgeneration due to oxygen deprivation then to reoxygenation is a major contributor to the mitochondrial OXPHOS electron leak at complexes I/II and to complex V ATP synthase dysfunction. These two alterations play, play a critical role in neuronal cell death, including apoptosis (112). In addition, mitochondrial NOXs are important O_2^- sources during I/R (112, 150, 151). Notably, although oxidative distress mediated by mitochondrial O_2^- is detrimental during I/R, oxidative eustress mediated by mitochondrial O_2^- plays a signaling role in activating antioxidant defense and cell survival in post-ischemic tissues (32, 112, 243, 258, 259, 267). In BBB endothelial cells, changes in H_2O_2 levels strongly regulate angiogenesis, permeability, and cell death (6). Oxidative eustress mediated by H_2O_2 induces endothelial tube formation and increases endothelial cell tube length, while oxidative distress mediated by H_2O_2 increases endothelial cell permeability and induces cytoskeleton disorganization and cell death apoptosis, although the cytoskeleton alteration starts during oxidative eustress (6). Moreover, mitochondrial calcium overload during I/R blocks H_2O_2 catabolism in the brain (112). Regarding the key enzymes, during I/R, SOD and catalase activities decrease in the brain, mainly in the hippocampus and striatum, while XOR and MPO activities, which is harmful to the patient (40, 103, 104). Altogether, during I/R, oxidative eustress mediated by ROS is beneficial while oxidative distress mediated by ROS and altered SOD, catalase, XOR and MPO enzymes is detrimental.

The RNS metabolism plays a critical role during I/R through both its reactive species and key NOS enzymes. Depending on cell types, levels, and sources, the NO can be either detrimental or beneficial in ischemic stroke (44). Following reperfusion, overgenerated NO by nNOS plays a rapid neurotoxic role (44, 85, 239). Hours after reperfusion, in microglia, astrocytes and endothelial cells, estimated at 1,000 times more than nNOS-related NO, NO overgenerated by activated iNOS also plays a neurotoxic role (44, 85, 239). In contrast, eNOS-related NO plays a neuroprotective role by interacting with ROS metabolism and

inducing collateral flow (44, 85, 239). Although the role played by NO is known to vary in ischemic stroke, the debate continues regarding the contribution of nNOS, iNOS, and eNOS, the time course of NO generation from the three NOS, and other factors (42, 44, 85). Moreover, oxidative distress mediated by ONOO⁻ is neurotoxic following ischemic stroke, and blocking it using triterpenoid saponin is suggested as a promising treatment to attenuate the deleterious effects (39). In ischemia, during I/R, the key NOS enzymes are essential regulators of both the detrimental and beneficial roles of NO, and oxidative distress mediated by ONOO⁻ is detrimental.

Hydrogen sulfide also contributes to maintaining cerebrovascular homeostasis, including in ischemia but still with controversial effects (66, 90, 112, 166). Indeed, in ischemia, oxidative eustress mediated by H₂S is beneficial while oxidative distress is detrimental, i.e. neurotoxic (66, 90, 112, 166). The benefits of H₂S beneficial effect are through anti-oxidation property *via* increasing GSH levels, anti-apoptosis by regulating calcium homeostasis and caspase status, anti-necrosis, and attenuation of the deleterious effects of I/R related to mitochondrial function (66, 90, 112). Benefits are also derived through the anti-inflammatory property *via* inhibiting the release of NO and pro-inflammatory cytokines and proangiogenic property by induction of the expression of the angiogenic factors angiopoietin-1 and VEGF (66, 90, 112). In contrast, the detrimental effect of H₂S is through glutamate excitotoxicity and brain edema by negatively modulating aquaporin 4 and matrix metalloproteinase 9 status (66, 90, 112).

Finally, the RCS family is negatively involved in ischemic stroke. In different organs, plasma and serum MGO, which triggers autophagy activation, accumulates along with as 4-HNE, considered a plasma biomarker of ischemic stroke, and MDA (33, 68, 73, 134, 169). In addition, activities of GPX, including GPX1 and PRDX, appear critical during and after ischemia, including related to neuroinflammation (57, 84, 108). Thus, in ischemia, oxidative distress mediated by RCS and key enzymes GPX and PRDX are detrimental.

During ischemia/reperfusion, oxidative eustress mediated by ROS and RSS, and oxidative distress mediated by eNOS-related NO are beneficial to counteract deleterious effects of I/R. Meanwhile, oxidative distress mediated by ROS, nNOs- and iNOS-related RNS, RSS, and RCS is detrimental. Notably, in other pathologies, key enzymes SOD, catalase, XOR, and MPO play essential redox roles during I/R (**Fig. 7**).

Why did antioxidant therapies fail to treat ischemia ?

Several therapies introduced to reduce the deleterious effects of I/R are promising. Specific upregulation of mitochondrial antioxidant enzymes Mn-SOD (SOD2) and PRDXs, inhibition of mitochondrial NOX, reduction of oxidative distress with specific mitochondrial antioxidants such as mitoquinone, modulation of mitochondrial redox status using specific microRNAs, and even ROS-scavenging nanoparticles are among the potential therapeutic pathways (112, 185). However, antioxidant therapies targeting ROS have been disappointing as results could not be successfully translated from animal models of stroke, including ischemic stroke, to clinical use (111, 117, 215, 255). For example, uric acid, a natural antioxidant that targets ROS and RNS peroxynitrite, ROS scavengers edavarone, tetramethylpyrazine, FR210575, and even nitrone NXY-059, were neuroprotective and succeeded in treating the deleterious effects of stroke in animal models but failed to prove efficacious at the clinical level (215, 255). After two large randomized and double-blinded clinical trials with more than 5,000 patients total, the promising nitrone NXY-059 did not show any bedside efficacy (215, 255). In addition, although the promising natural plant extracts Egb-761® or Tanakan® from *Ginkgo biloba* with antioxidant terpenes and flavonoids had neuroprotective effects in animal stroke models, clinical trials did not confirm the results, and larger and robust trials are needed (111, 255). The rationale for using antioxidant therapy in addition to other therapy against stroke, including ischemic stroke, is to potentially prevent long-term neurodegeneration post-stroke by decreasing the risk of Alzheimer's disease (AD) through the reduction of oxidative stress (117).

So, why did antioxidant therapies fail to treat ischemia ? First, animal model success does not always translate to clinical trial and bedside success due to differences in complexity, physiology and pathology, including symptoms and alterations (21). Second, importantly, antioxidant therapies fail due to disappointing targets. Targeting only ROS or RNS is insufficient when the entire RSI is involved with its many reactive species and key enzymes. Targeting ROS, RNS, RSS, and RCS together, considering oxidative eustress and distress effects, and modulating SOD, catalase, XOR, MPO, GPXs, and PRDXs enzymes will be the most powerful therapy to treat ischemia. Regulating the entire RSI will induce key enzyme remodeling, and the best therapy will be one molecule or a combination of molecules directly targeting the heart of the RSI. Therefore, we strongly encourage

increased research to better understand the RSI related to the pathophysiology of stroke as the first step to discover the best therapy.

The RSI in neurodegenerative disorders

Oxidative distress, bioenergetic metabolism, senescence, and cell death are intriguing and complex key players involved in the so-called neurodegenerative disorders, the leading cause of disability worldwide and a major cause of global deaths. These disorders include Parkinson's disease (PD), AD, vascular dementia, frontotemporal dementia, amyotrophic lateral sclerosis (ALS), Huntington's disease and spinocerebellar ataxias (14, 32, 75, 81, 153, 232). Adult neurogenetic alteration and neuroinflammation are also involved in neurodegenerative disorders (14, 32, 75, 81, 153, 232) (**Fig. 8**).

At the molecular level, most neurodegenerative disorders share pathways focusing on mitochondrial function, oxidative distress, autophagy-lysosome pathway, protein quality control machinery, and finally, neuronal death, therefore implying the involvement of multiple complex biomarkers (81, 204). For example, neuronal death is the PD hallmark mediated by intracellular accumulation and aggregation of the presynaptic protein α -synuclein in Lewy bodies (153). Furthermore, both neuronal death and synapse degeneration are AD hallmarks mediated by amyloid- β (A β) clearance processing impairment and phosphorylated tau (pTau) neurofibrillary tangle aggregation (153). In addition, mitochondrial function, calcium homeostasis, lysosome, and, importantly, redox balance play crucial roles in both neurodegenerative disorders (153). Mitochondrial dysfunction and oxidative distress are promising targets alone or combined to treat several neurodegenerative disorders, including AD and PD (36, 153, 204, 252, 253).

One significant unknown is whether oxidative distress is a cause or consequence of neurodegeneration (7). A better understanding of the RSI, including RCS and the key enzymes, will help answer this question and discover new therapies to treat neurodegenerative disorders, including ALS, PD, and AD (**Fig.8**).

First, related to mitochondrial uncoupling and mitochondrial calcium concentration, oxidative distress mediated by O_2^- is associated with AD (262). Oxidative distress mediated by H_2O_2 occurs during the early stages of protein aggregation in AD and dementia (237). In addition, reduced GSH levels are found in ALS, AD and PD (167). Importantly, the key

enzymes SOD, catalase, XOR, and MPO also play complex and crucial roles in neurodegenerative disorders including ALS, AD, and PD (167). Reduction of both SOD and catalase activities are found in ALS, while SOD levels increase in PD (167). In AD, SOD levels increase in the hippocampus and amygdala while SOD and catalase levels decrease in the frontal and temporal cortex (167). Inhibition of XOR by oxypurinol (alloxanthine) in a mouse model of AD and by allopurinol in the rat model of PD reduces oxidative distress mediated by ROS, thus suggesting a key role for XOR at least in those neurodegenerative disorders (82). Moreover, in neurodegenerative disorders, including ALS, AD, and PD, increased MPO activity is detrimental (194). Oxidative distress mediated by ROS, in addition to alterations in key enzymes SOD, catalase, XOR and MPO, are detrimental to neurodegenerative disorders.

The RNS metabolism is also involved in neurodegenerative disorders. Overgeneration of NO and related ONOO⁻ is associated with neurodegeneration through a close link with iron homeostasis, which regulates ferroptosis, brain oxygenation, mitochondrial function, neurotransmitter metabolism, and compact myelin formation (140, 227). Nitric oxide also regulates iron homeostasis at a minimum through ferritin and ferroportin, and iron levels are strongly increased in A β plaques and tau tangles of AD patients and the SN of PD patients (139, 140, 162). In AD, iNOS, eNOSs and nNOS increases are associated with A β deposits in the brain and reduced NO bioavailability in plasma (167). In addition, glutamate, the most abundant neurotransmitter in excess in neurodegenerative disorders, initiates NO overgeneration by nNOS, which strongly induces demyelination, i.e. the loss of myelin (139, 140, 162). Thus, in neurodegenerative disorders, oxidative distress mediated by RNS is detrimental.

In addition to ROS and RNS, RSS metabolism must be considered when studying neurodegenerative disorders. Hydrogen sulfide is attracting much attention in neurodegenerative disorder research through its effects on neuroinflammation, neurodegeneration-related MAO linked to catecholamines, NMDA potentiation linked to glutamate, potassium channels, calcium channel activity, and finally, oxidative distress (25, 182, 200). In the brain, H₂S levels are reduced in AD and PD (182). Interestingly, H₂S also inhibits the NO-related angiogenic effect, just as NO inhibits the enzymatic effect of H₂S by modulating the activity of the H₂S-producing CBS enzyme (25, 182, 200). Moreover, NO,

H₂S suppresses A β plaque formation and deposits in microvessels, including in the brain (25, 182, 200). Although very high levels of RSS are neurotoxic, oxidative distress mediated by RSS is beneficial in fighting neurodegenerative disorders.

Finally, oxidative distress mediated by RCS and key GPX and PRDX enzyme breakdown is detrimental to neurodegenerative disorders. Overgenerated by an excess of lipid peroxidation, MGO, 4-HNE and MDA accumulate in the brain of ALS, PD and AD patients, thus resulting in the formation of advanced glycation end-products (AGEs) (60, 77, 167, 231). In addition, GPXs and PRDXs appear to play important roles in neurodegenerative disorders as neurodegeneration is associated with GPXs and PRDXs breakdown. Although it is unclear if GPXs levels either increase, decrease, or do not change in ALS, both GPX1 and GPX4, new players in neurodegeneration, are promising targets to activate in PD and AD (30, 167, 214). Activation of PRDXs enzymes is also a promising therapy for ALS, PD, and AD (234).

Present evidence suggests that in neurodegenerative disorders including ALS, PD, and AD, oxidative distress mediated by ROS, RNS, and RCS and altered SOD, catalase, XOR, MPO, GPXs, and PRDXs are detrimental. Interestingly, oxidative distress mediated by RSS is beneficial in the fight against neurodegenerative disorders, although high levels of H₂S should be addressed carefully to limit neurotoxic side effects. Once again, the entire RSI, including RCS and the key enzymes, are major players in neurodegeneration and should be considered together in future studies (**Fig. 8**).

The RSI is a promising target for the treatment of neurodegenerative disorders

Researchers in the neurodegenerative disorder and antioxidant fields need to face the difficult truth that current antioxidant therapies available to treat neurodegenerative disorders have been less than successful. Indeed, all the tested antioxidant drugs that tend to reduce oxidative distress mediated by ROS, increase GSH levels, and increase SOD and catalase activities from *in vitro* to animal models, ultimately failed at clinical trial levels (167). These include edavarone, SOD/catalase mimetics EUK-8 and EUK-134 in ALS, valproic acid, melatonin, selegiline, deferoxamine in PD, vitamin C, resveratrol and curcumin in AD, coenzyme Q10 in PD and AD, and vitamin E (tocopherol) in ALS, PD and AD and PD (167).

Complexity is one likely reason why a loss in translation occurs from animal models to human physiology (21). Targeting only one reactive species family is not sufficient. The most powerful therapy for neurodegenerative disorders will target ROS, RNS, RSS, and RCS together and the key enzymes that act upon them. Therefore, we strongly encourage the research community to improve their understanding of the RSI related to the pathophysiology of neurodegenerative disorders including ALS, PD, and AD, as the first step to discovering the best therapy.

The RSI in brain cancers

Aging is the biggest risk factor for cancer, which is a leading cause of death globally (56). Cancer is a group of more than 100 malignant diseases throughout the body in which cells grow uncontrollably (56, 125). Glioma accounts for 80% of malignant primary brain cancers (129). They are categorized into three types: oligodendroglioma, ependymoma, and astrocytoma, including the most frequent and the most lethal primary brain cancers, the glioblastoma (129). In addition, it is estimated that malignant secondary brain cancers, called brain metastases, occur in 20% of all the patients with primary cancer with other origins, mainly lung, breast, colorectal, and melanoma cancers (1). In primary brain cancers and metastases, coordination between bioenergetic metabolism and hypoxia plays a critical and harmful role in carcinogenesis, cancer progression, and cancer cell dissemination (22, 98, 179) (**Fig. 9**).

Interestingly, hypoxia which results from the disequilibrium between oxygen delivery and consumption, is a pervasive stimulus at physiological and pathophysiological levels, including in cancer (3, 67, 163). Hypoxia induces metabolic changes in the cancer cell, in cancer stem cell quiescence, a reversible state of non-dividing cells that retain their ability to re-enter cell division, and ultimately, in cancer growth, including in glioblastoma and anticancer therapy resistance such as radiotherapy (3, 10, 67, 88, 163). Associated with hypoxia, the redox homeostasis dysregulation, one of the hallmarks of cancer, increases in antioxidant defense, increases ROS levels, inactivates apoptosis, and provides a metabolic switch from mitochondrial OXPHOS to glycolysis, presenting a complicated picture for anticancer therapies (179). Hypoxia is of particular interest and a still complicated feature

in cancer, including brain cancers. Obviously, regarding reactive species, the first concern is always to minimize ROS (**Fig. 9**).

First, one major concern in cancer, including in the brain, is whether hypoxia modulates ROS generation and whether ROS induce HIF stabilization. Stabilized HIF-1 α subunit is translocated to mitochondria to reduce O₂⁻ generation and attenuate mitochondrial dysfunction by improving the OXPHOS function at complex IV by regulating mitochondrial-selective autophagy, and likely by regulating mitochondrial DNA transcription (136). In addition, stabilized HIF-2 stimulates antioxidant gene expression including the nuclear transcription factor erythroid-2-related factor 2 to reduce O₂⁻ generation in macrophages while mitochondrial O₂⁻ is required to stabilize HIF-2 (58, 212). Moreover, hypoxia induces H₂O₂ overgeneration (including in cancer), and overgenerated H₂O₂ induces stabilization of hypoxia factor and related pathways (3, 11, 67, 116). Notably, it has been recently suggested that H₂O₂ determines the glioma's fate, including in anticancer therapy such as chemotherapy and radiotherapy (280). Finally, in brain glioma, in the hypoxic condition, activities of key enzymes SOD and catalase are reduced while XOR and MPO activities are increased to the detriment of the patient (93, 126, 193). Oxidative distress is pro-cancer when associated with transcriptional factors HIFs and related pathways mediated by ROS and altered SOD, catalase, XOR, and MPO.

In cancer, including that in the brain, RNS metabolism also contributes to regulating the hypoxic status and effects (89). Immune system evasion and anticancer therapy resistance occur in part due to NO overgeneration induced by hypoxia (17, 24). In glioma, an increase in iNOS expression is a hallmark of neuroinflammation and of chemoresistance, and iNOS expression and activity inhibitors are promising anti-glioma agents (148). Numerous studies showed that NO regulates glioma growth, cancer angiogenesis, cancer cell invasion, radio- and chemoresistance (5, 226, 235, 242). In addition, ONOO⁻ accumulation in glioblastoma inactivates wild-type p53 function and is associated with an altered inflammatory response in the glioma microenvironment (51). In brain cancer, oxidative distress mediated by RNS is pro-cancer.

Reactive sulfur species metabolism is as important as ROS and RNS in cancer. In brain cancer, associated with hypoxia, oxidative distress mediated by RSS is pro-cancer, although

RSS may be promising radiosensitizers depending on their concentration. Hydrogen sulfide has been suggested as a promising radiosensitizer, at least for glioblastoma cells through selective OXPHOS complex III impairment and mitochondrial respiration reduction, an increase in H₂O₂ levels, and an increase in DNA damage (265). However, H₂S also favors C6 glioma cell proliferation and survival through increased cyclooxygenase-2 expression and apoptosis reduction (278). The debate surrounding the anti-cancer and pro-cancer roles of H₂S in brain cancers is made more complicated by the puzzling increase in expression of the H₂S producing enzymes CBS and CSE in astrocytomas and brain metastases (132). Hypoxia increases this complexity, as hypoxia induces H₂S generation, and H₂S regulates HIF-1 α subunit expression and stabilization (257).

Finally, RCS metabolism also plays a key role in cancer, including in the brain. Methylglyoxal induces cell cycle arrest, inhibits cell proliferation, and initiates apoptosis in glioblastoma cells (186). Interestingly, in glioblastoma, 4-HNE and MDA levels decrease, related to high aldehyde dehydrogenase 1A3 levels, which detoxify cancer cells from aldehydes (190, 261). In addition, in glioma, key enzyme GPX activity decreases, while a high level of GPX2 is a poor prognosis biomarker in glioblastoma (95, 193). Finally, an increase in PRDX4 activity in glioblastoma promotes cancer proliferation and anticancer therapy resistance (184). Thus, targeting GPX and PRDX as well as inducing oxidative distress mediated by RCS could be promising anti-cancer therapies, including against glioblastoma.

Once again, in brain cancer, the entire RSI is the ideal target through the coordination of the different reactive species and key enzymes (**Fig. 9**). In the brain, associated with hypoxia, oxidative distress mediated by ROS, RNS, and RSS is pro-cancer, while inducing oxidative distress mediated by RCS is a promising anti-cancer therapy. Additionally, altered SOD, catalase, XOR, MPO, GPX, and PRDX enzymes are promising targets in anti-cancer therapy, including brain cancer.

Antioxidants and cancer: bad and good news

Anti-ROS antioxidants such as N-acetylcysteine (NAC) and vitamin E, at high concentrations, accelerate lung cancer by disrupting the ROS-p53 axis, as p53 is a tumor suppressor gene involved in stress response following oxidative stress, hypoxia and

ionizing radiation (131, 203). At high levels, NAC and vitamin E also favor malignant melanoma progression and metastasis by deregulating the equilibrium between GSH and GSSG (131, 203). Once again, associated with hypoxia, the delicate equilibrium between reactive species and the antioxidant defense in cancer, including in the brain, is not linked to only ROS. This delicate equilibrium is linked to ROS, RNS, RSS, RCS, and the key enzymes amid the RSI.

A final example of antioxidant activity in many types of cancer is the frequent gain-of-function mutations of the so-called isocitrate dehydrogenase-1 (IDH1) and -2 (IDH2). These enzymes participate in the Krebs cycle, are implicated in multiple metabolic processes and produce NADPH (NAD phosphate) and α -KG (α -ketoglutarate) (110, 267). In cancer, mutated IDH1 and IDH2 reduce NADPH and α -KG generation by losing their normal catalytic activity and overproduce 2-hydroxyglutarate (2-HG) by gaining a new function (119). The oncometabolite 2-HG, an antagonist of α -KG, reduces histone and DNA demethylation, promotes cancer microenvironment formation through VEGF upregulation, increases HIF-1 α subunit stability, increases ROS generation, and dysregulates H₂S generation (105, 106, 110, 123, 144, 260, 267). Thus, gain-of-function mutated IDH1 and IDH2 in cancers (including primary brain cancers) that account for more than 70-80% of lower-grade glioma and the majority of secondary glioblastoma, induce epigenetic reprogramming, bioenergetic metabolism dysregulation (at least both ROS and RSS dysregulation) and finally cancer invasion (105, 106, 110, 123, 144, 260, 267). Reactive species interactome should be considered to ultimately design more efficient and powerful anti-cancer therapies in all cancers. Combining RSI modulation therapy with radiotherapy, chemotherapy, nanoparticle therapy and/or immunotherapy may provide especially promising pathways.

Conclusion on the RSI in brain pathology

Through depression, ischemia, neurodegenerative disorders, and cancers in the brain, we demonstrated that the entire RSI, including RCS and key enzymes, should be considered together instead of only one reactive species family. In depression, oxidative distress mediated by ROS, RNS and RCS exerts a pro-depressant effect, while oxidative distress mediated by RSS exerts an anti-depressant effect. In ischemia, oxidative eustress mediated

by ROS and RSS and oxidative distress mediated by eNOS-related NO are beneficial to counteract deleterious effects, while oxidative distress mediated by ROS, nNOS- and iNOS-related RNS, RSS, and RCS are detrimental. In neurodegenerative disorders, oxidative distress mediated by ROS, RNS, and RCS is detrimental, while oxidative distress mediated by RSS is beneficial to fight neurodegenerative disorders, although high levels of H₂S should be cautiously addressed to limit neurotoxic side effects. Finally, in brain cancer, associated with hypoxia, oxidative distress mediated by ROS, RNS, and RSS is detrimental, while inducing oxidative distress mediated by RCS is a promising anti-cancer therapy. Importantly, in addition to the reactive species, the key enzymes SOD, catalase, XOR, MPO, GPX, and PRDX should be considered in all these brain pathologies.

In a pathological process, what creates the global redox effect is the combination between (1) effects from different reactive species families in different concentrations, (2) interactions between the different families, and (3) activities of key enzymes that contribute to the RSI dynamics. The RSI, including RCS and key enzymes, is fully committed in brain pathologies.

Conclusions

Oxidative eustress and distress must be seriously considered in relation to reactive species concentrations. From the most studied ROS, it appears that the reactive species interactome (RSI) in its entirety has to be seriously considered related to reactive species identification and interactions. We highlighted that the RSI, meaning ROS, RNS, RSS, RCS and key associated enzymes, is fully committed in brain physiology and pathology (**Fig. 10**). Depending on organ oxygenation, physiology, pathology, and key enzyme dynamics, the complex coordination of the four reactive species families related to their concentrations creates the global redox effect. The ROS, RNS, RSS, and RCS form a link between physiology and pathologies, between the antioxidant defense and the bioenergetic metabolism, between cell death and cell survival. From adult neurogenesis to cell death, aging, depression, ischemia, neurodegeneration, and finally, cancers, the brain is a vital organ in which the RSI combined in eustress or distress is playing all its potential for mechanistic and therapeutic clues.

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EM and LC wrote the manuscript with support and input from SV, MB and EP, LC supervised the project. All authors discussed the forum review article and contributed to the final manuscript.

Authorship confirmation statement

All authors confirm that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. All authors confirm that the manuscript has been read and approved by all authors and that there are no other persons who satisfied the criteria for authorship but are not listed. All authors confirm that the order of authors listed in the manuscript has been approved by all authors. All authors understand that the Corresponding Author is the sole contact for the Editorial process regarding communication, progress, submission(s) of revision(s) and final approval of proofs.

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Abbreviations, Symbols and Terminology

α -KG Alpha-ketoglutarate

2-HG 2-Hydroxyglutarate

3-MST 3-Mercatopyruvate sulfurtransferase

4-HNE 4-hydroxy-trans-2-nonenal
A β Amyloid-beta
AD Alzheimer's disease
AGEs Advanced glycation end products
ALEs Lipoxidation end products
ALS Amyotrophic lateral sclerosis
AST Aspartate aminotransferase
ATP Adenosine triphosphate
BBB Blood-brain barrier
BCL2 B-Cell Lymphoma 2
BDNF Brain-derived neurotrophic factor
BH4 Tetrahydrobiopterin
CAT Cysteine aminotransferase
CBS Cystathionine b-synthase
CSE/CGL Cystathionine-gamma-Lyase
Cu⁺ Cuprous ion
Cu²⁺ Cupric ion
DCX Doublecortin
DHAP Dihydroxyacetone-phosphate
DHLA Dihydrolipoic acid
DNA DesoxyriboNucleic acid
DTT Dithiothreitol
ER Endoplasmic Reticulum
ERK 1/2 Extracellular signal-regulated Kinase 1/2
FAD Flavin adenine dinucleotide
Fe²⁺ Ferrous ion
Fe³⁺ Ferric ion
FMN Flavin mononucleotide
FOXO3 Forkhead box O3
GFAP Glial Fibrillary Acidic Protein
GO Glyoxal

GOT Glutamate oxaloacetate transaminase
G3P Glyceraldehyde-3-phosphate
GPX Glutathione peroxidase
GSH reduced Glutathione
GSSG oxidized Glutathione
H₂O Dihydrogen monoxide
H₂O₂ Hydrogen peroxide
H₂S Hydrogen sulfide
H₂S₂ Hydrogen disulfide, Persulfide
H₂S₃ Trisulfane
H₂S₅ Pentasulfane
H₂S_n Hydrogen polysulfide
HIF-1 α Hypoxia-inducible factor 1-alpha
HIF-2 Hypoxia-inducible factor 2
HOCl Hypochlorous acid
HSP90 Heat Shock Protein 90
I/R Ischemia/Reperfusion
IDH1 Isocitrate DeHydrogenase-1
NAC N-acetylcysteine
MDA Malondialdehyde
MGO Methylglyoxal
MMO Monooxygenase
Mn³⁺ Manganese ion
MPO Myeloperoxidase
NADPH Nicotinamide Adenine Dinucleotide Phosphate
NaN₃ Sodium azide
Nestin Neuroepithelial stem cell protein
NEUROD Neurogenic differentiation
NF-KB Nuclear factor Kappa-light-chain-enhancer of activated B cells
NSC Neural stem cell
NiR Nitrite reductase

NO Nitric oxide
NO₂ Nitrogen dioxide
NO₂⁻ Nitrite
NO₃⁻ Nitrate
NOS Nitric oxide synthase
NOX NADPH oxidase
NR Nitrate reductase
NMDA N-Methyl-D-Aspartate acid
NMDARs N-methyl-D-Aspartate Receptors
O₂ molecular oxygen
O₂⁻ Anion superoxide
OH[·] Hydroxyl radicals
ONOO⁻ Peroxynitrite
OXPHOS Oxidative Phosphorylation
P53 Tumor protein 53
PD Parkinson's Disease
PI3K Phosphoinositide 3-Kinase
PRDX Peroxiredoxin
PTEN Phosphatase and tensin Homolog
PUFAs PolyUnsaturated Fatty Acids
RCS Reactive Carbonyl Species
RIP1 Receptor-interacting protein kinase 1
RNS Reactive Nitrogen Species
RNA Ribonucleic acid
ROS Reactive Oxygen Species
RSH Thiol
RSI Reactive Species Interactome
RSS Reactive Sulfur Species
S₂O₃²⁻ Thiosulfate
SA-β-gal Senescence-Associated Beta-Galactosidase
SASP Senescence-Associated Secretory Phenotype

SIRT1 Sirtuin 1

SOD Superoxide dismutase

SOX2 Sex-determining region Y box 2

TRX Thioredoxin

UO Urate oxidase

VEGF Vascular Endothelial Growth Factor

XOR Xanthine OxidoReductase

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Figure Legends

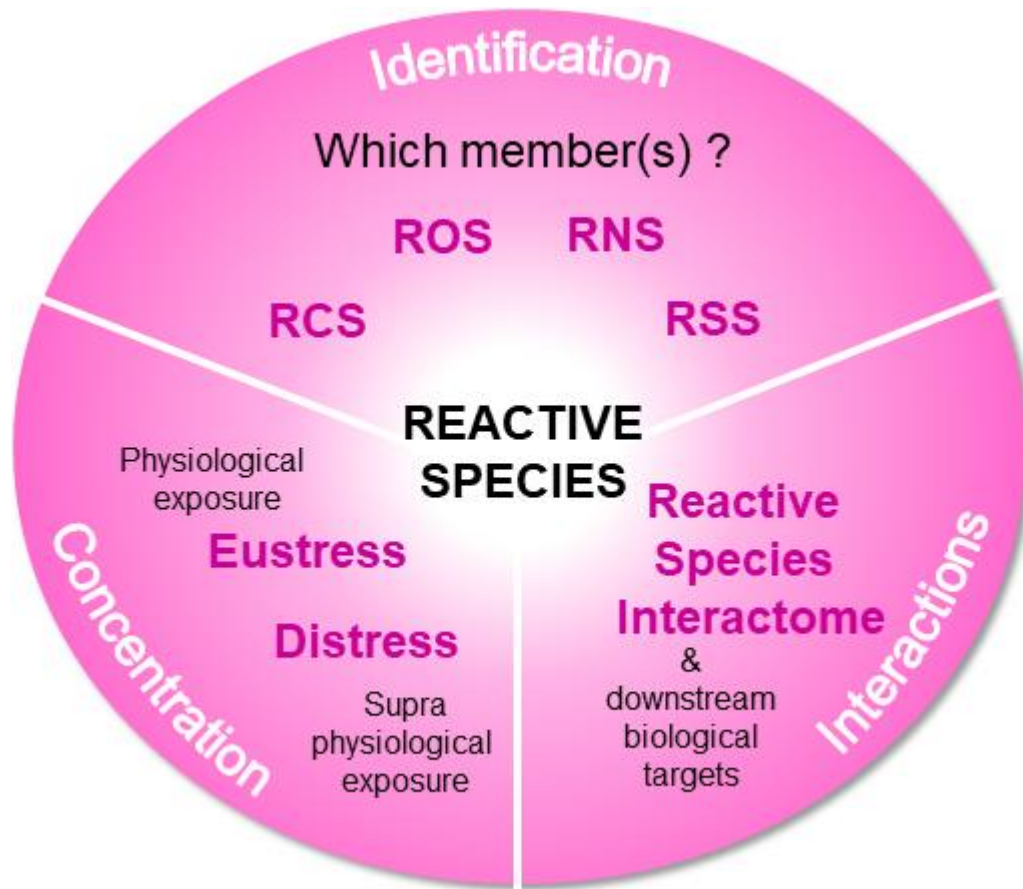


Figure 1. United view to improve the understanding of reactive species in physiology and pathology. The most important elements are 1) the identification of the reactive species, i.e. identification, 2) concentration-dependent functions through oxidative eustress and distress, i.e. concentration, and 3) the dynamic interaction of the reactive species between themselves and downstream biological targets through the reactive species interactome, i.e. interaction. RCS, reactive carbonyl species; RNS, reactive nitrogen species; ROS, reactive oxygen species; RSS, reactive sulfur species.

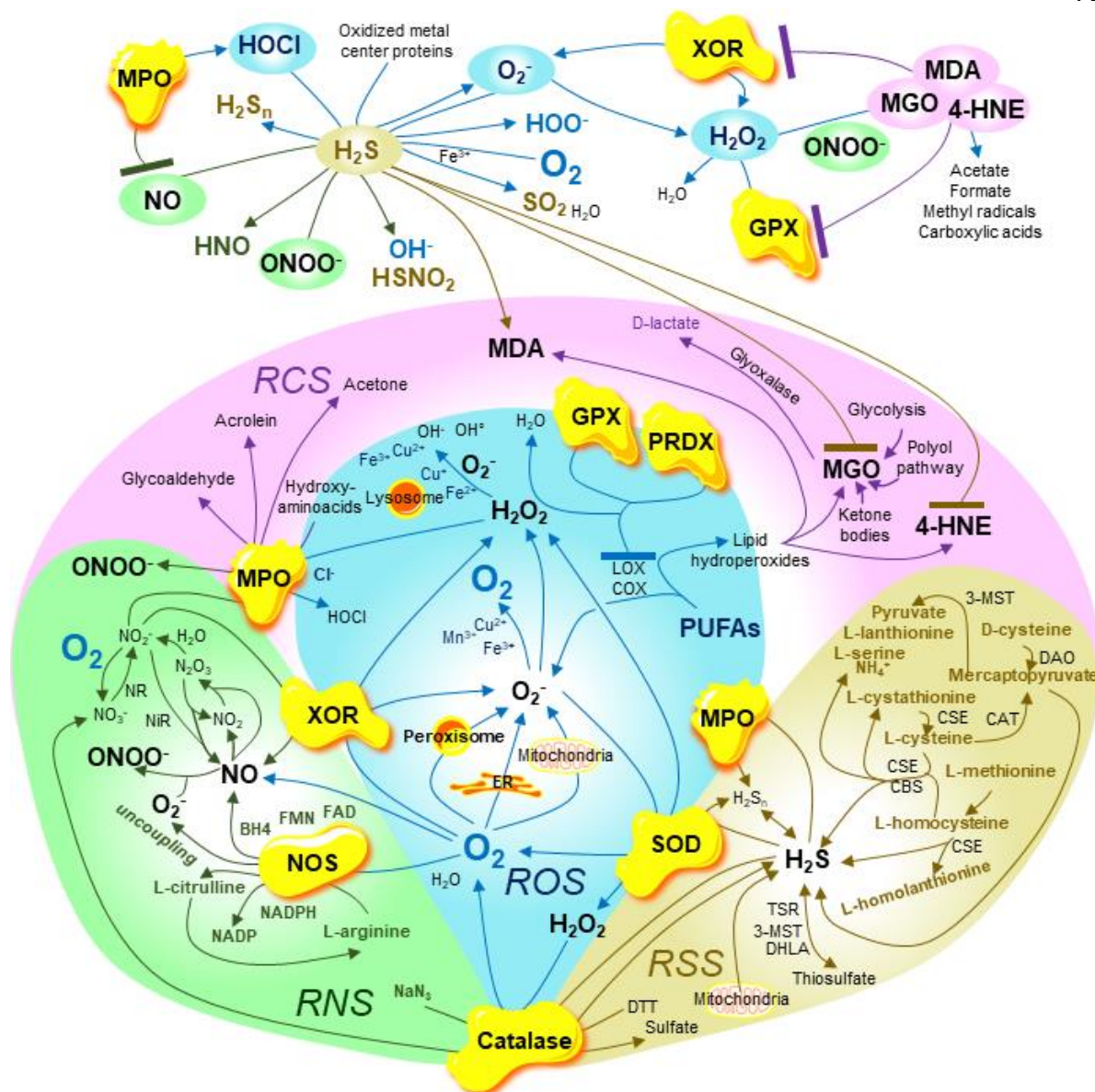


Figure 2. Main endogenous sources, interactions and enzymes of ROS, RNS, RSS, RCS. In a non-exhaustive manner, we overview the main endogenous sources and interactions of notable ROS, RNS, RSS, and RCS. Although the reactive species interactome initially focused on ROS, RNS, and RSS, we propose including the neglected RCS family to improve the understanding of reactive species. Presented key enzymes within ROS, RNS, RSS, and RCS metabolism strengthen the relationship between the four families. GPX, glutathione peroxidase; MPO, myeloperoxidase; NOS, nitric oxide synthase; PRDX, peroxiredoxin; SOD, superoxide dismutase; XOR, xanthine oxidoreductase.

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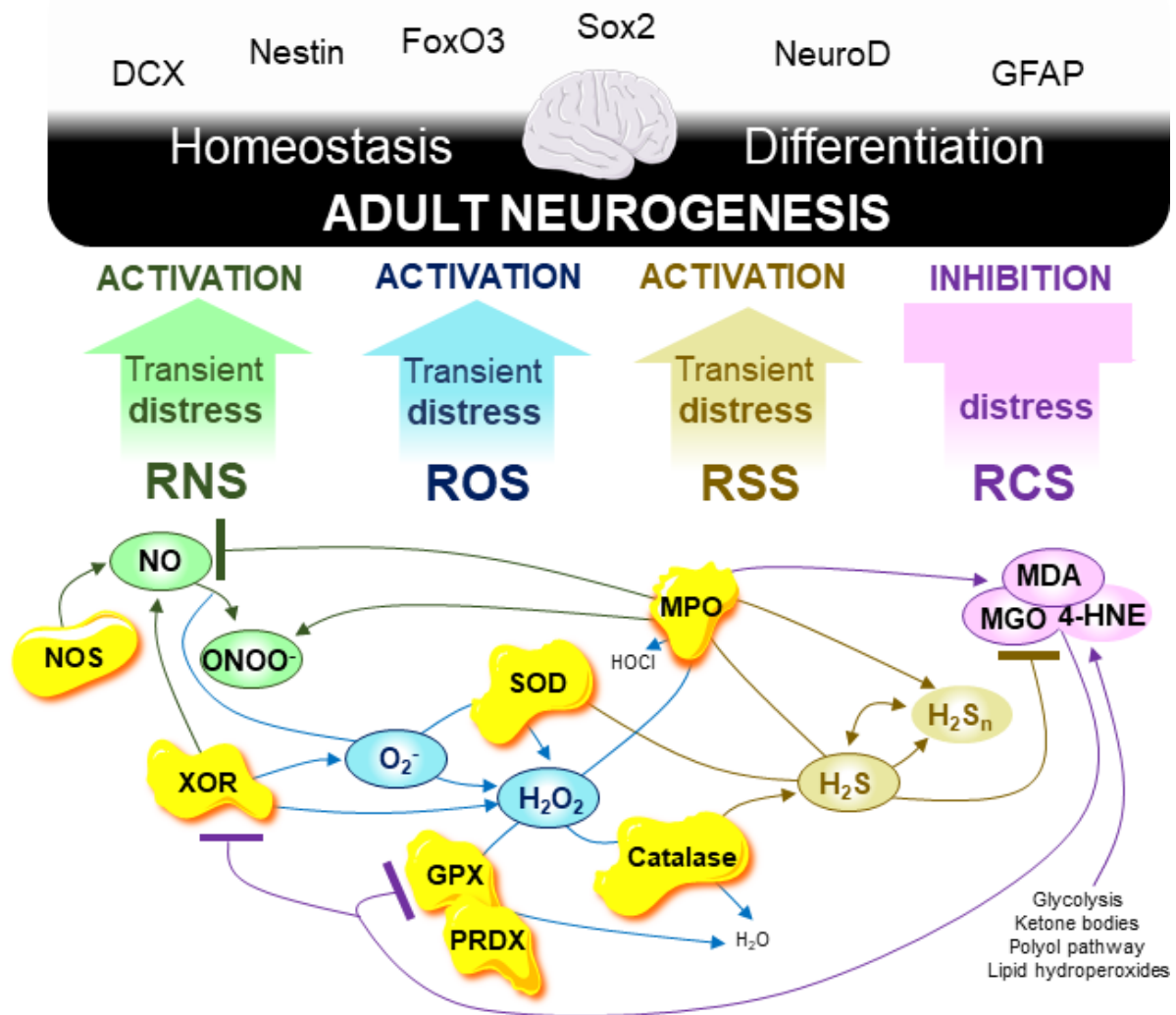


Figure 3. Notable reactive species and key enzymes in brain adult neurogenesis. Transient oxidative distress mediated by RNS, ROS, and RSS activates adult neurogenesis, while oxidative distress mediated by RCS inhibits adult neurogenesis. Although key biomarkers are involved in adult neurogenesis, including cell homeostasis, proliferation, and differentiation, the molecular mechanisms between reactive species and these biomarkers require further investigation. Key enzymes within reactive species dynamics could be of interest to improve the understanding of the roles of reactive species in adult neurogenesis. Circled reactive species are the known species involved in adult neurogenesis. GPX, glutathione peroxidase; MPO, myeloperoxidase; NOS, nitric oxide synthase; PRDX, peroxiredoxin; SOD, superoxide dismutase; XOR, xanthine oxidoreductase.

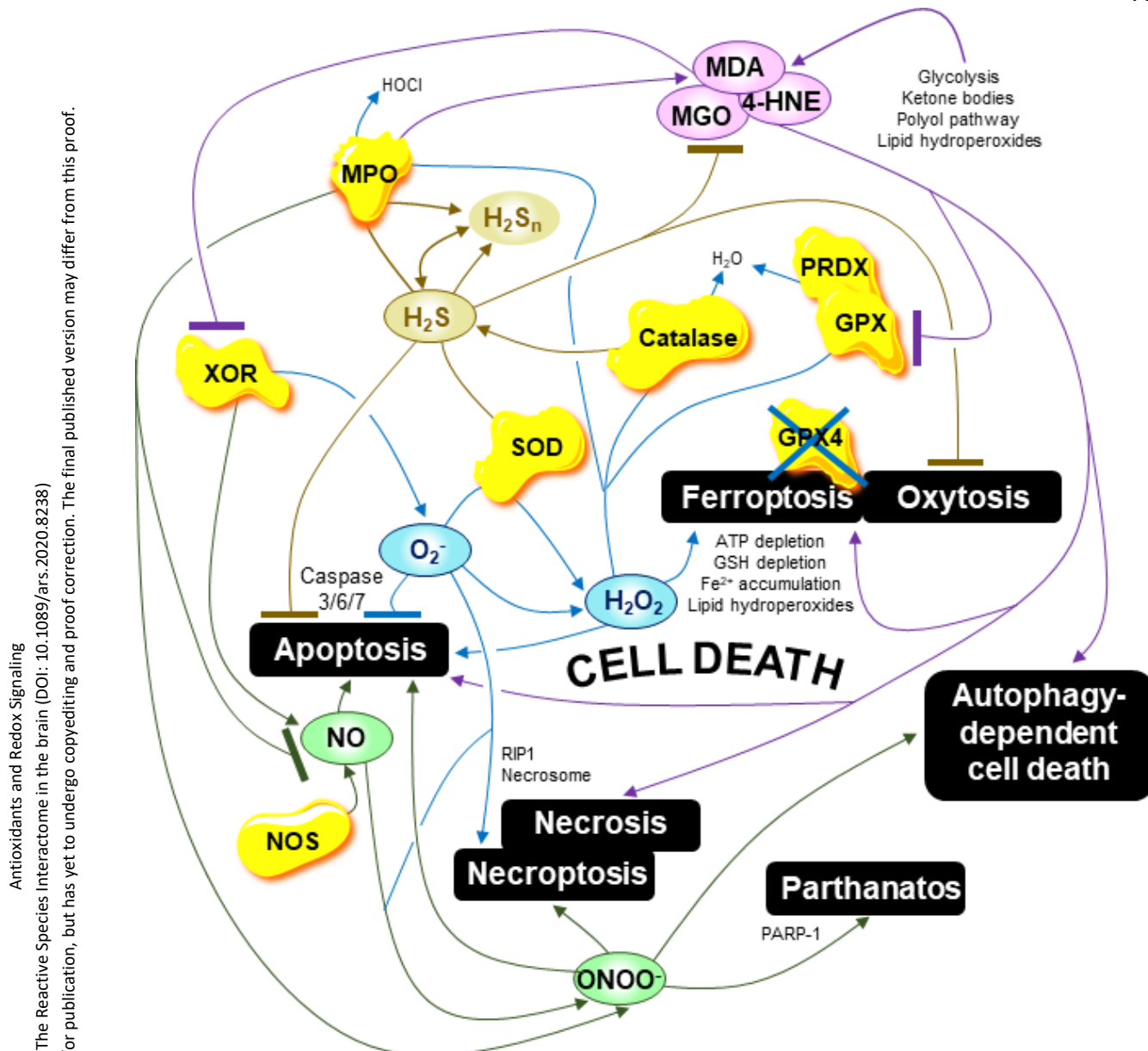


Figure 4. Notable reactive species and key enzymes in brain cell-death types. Among more than ten different cell-death types, several ROS, RNS, RSS, and RCS are key modulators, inducers or inhibitors, including apoptosis, oxytosis, ferroptosis, necrosis, including necroptosis, parthanatos and autophagy-dependent cell death. The integration of key enzymes within reactive species could improve the understanding of the roles of reactive species in major cell-death types in the brain, in physiology and pathology. Circled reactive species are the known species involved in cell-death types. GPX, glutathione peroxidase; MPO, myeloperoxidase; NOS, nitric oxide synthase; PARP-1, poly ADP-ribose polymerase 1; PRDX, peroxiredoxin; RIP1, receptor-interacting protein kinase 1; SOD, superoxide dismutase; XOR, xanthine oxidoreductase.

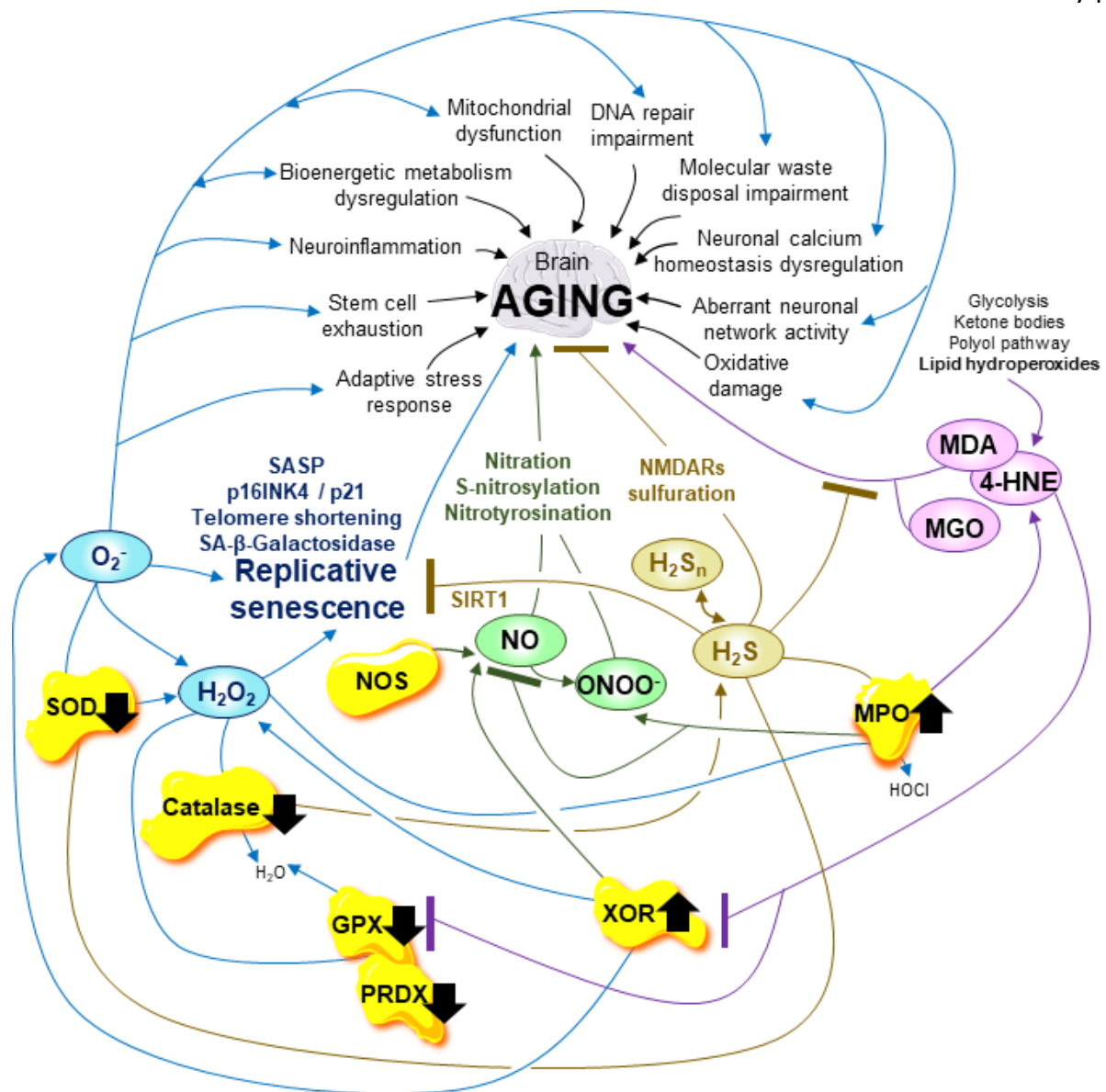


Figure 5. Is dysregulated reactive species interactome including RCS the eleventh hallmark of brain aging ? Oxidative distress mediated by ROS, RNS, and RCS are pro-aging, while oxidative distress mediated by RSS is anti-aging. Moreover, during brain aging, several key enzyme activities decline, including SOD and catalase, while other increase, including XOR and MPO. Therefore, improving the understanding of the roles of reactive species during brain aging needs further investigation considering key enzymes within. Circled reactive species are the known species involved in brain aging. GPX, glutathione peroxidase; MPO, myeloperoxidase; NOS, nitric oxide synthase; PRDX, peroxiredoxin; SOD, superoxide dismutase; XOR, xanthine oxidoreductase.

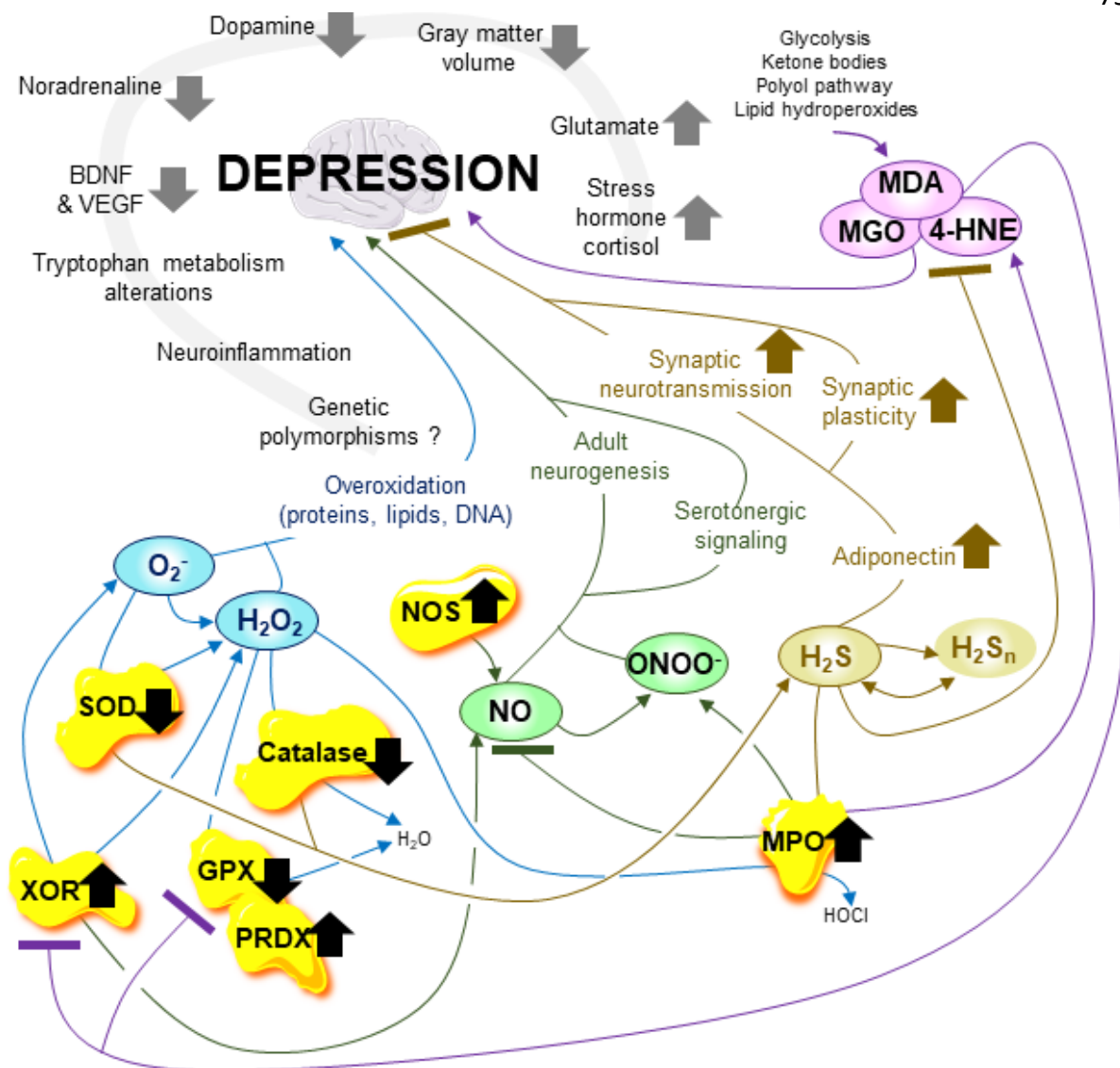


Figure 6. Notable reactive species and key enzymes in the mental disorder depression.

The leading mental disorder depression, which affects 300 million people worldwide, could be the second leading cause of illness worldwide by 2030. More than fifteen predictive biomarkers, and still a complex disease to treat. Oxidative distress mediated by RSS exerts an anti-depressant effect, while oxidative distress mediated by ROS, RNS, and RCS exerts a pro-depressant effect. The community is encouraged to improve the understanding of reactive species and key enzymes within in the mental disorder depression. Circled reactive species are the known species involved in depression. BDNF, brain-derived neurotrophic factor; GPX, glutathione peroxidase; MPO, myeloperoxidase; NOS, nitric oxide synthase; PRDX, peroxiredoxin; SOD, superoxide dismutase; VEGF, vascular endothelial growth factor; XOR, xanthine oxidoreductase.

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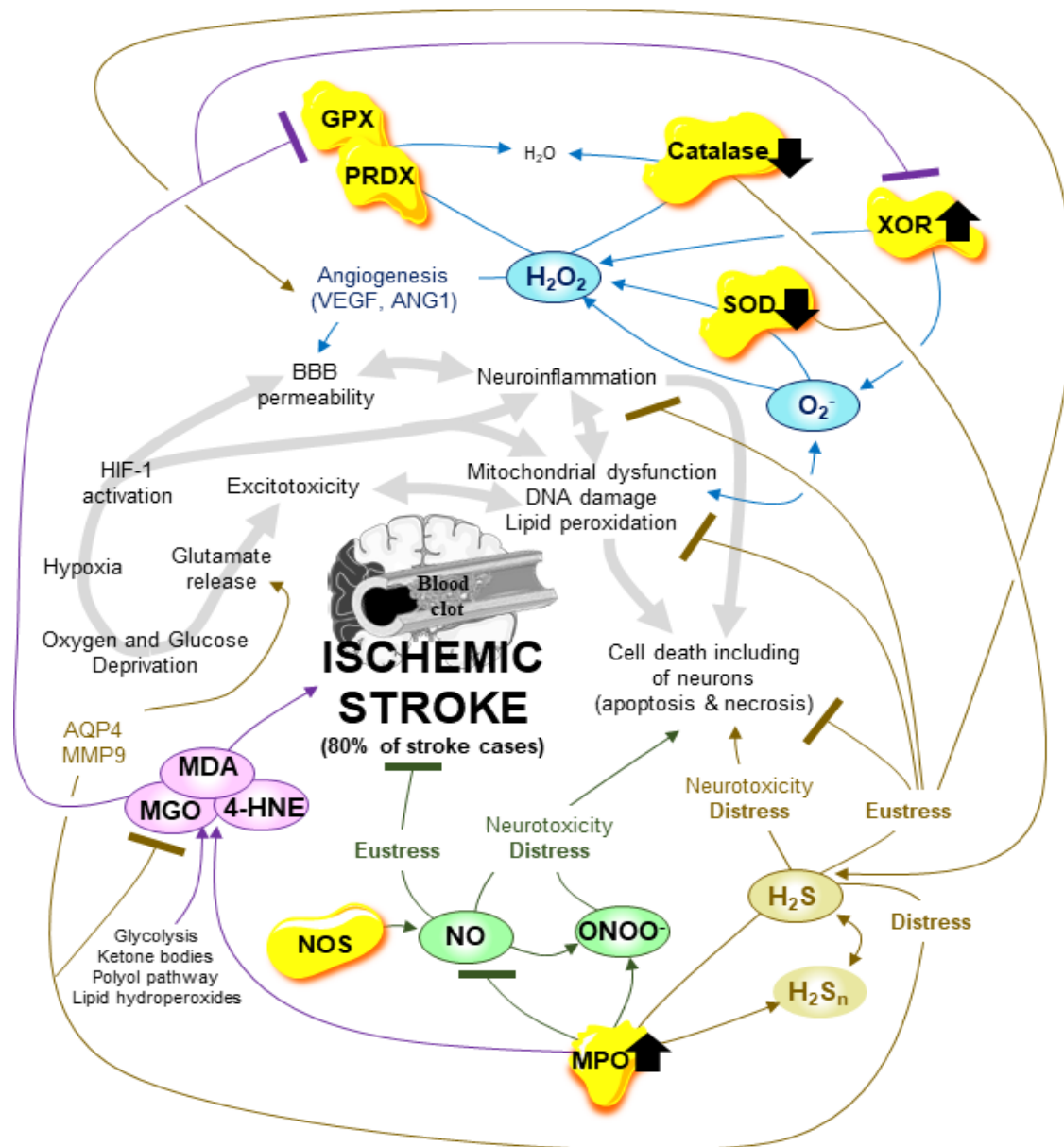


Figure 7. Notable reactive species and key enzymes in ischemic stroke. During ischemia/reperfusion, oxidative eustress mediated by ROS, RNS NO, and RSS is beneficial to counteract deleterious effects, while oxidative distress mediated by ROS, RNS, RSS, and RCS is detrimental. Notably, key enzymes catalase, SOD, MPO, and XOR play essential roles and are of great interest to improve the understanding the roles of reactive species in ischemic stroke. Circled reactive species are the known species involved in ischemic stroke. ANG1, angiotensin-1; AQP4, aquaporin 4; BBB, blood-brain barrier; GPX, glutathione peroxidase; MMP9, matrix metalloproteinase 9; MPO, myeloperoxidase; NOS, nitric oxide synthase; PRDX, peroxiredoxin; SOD, superoxide dismutase; XOR, xanthine oxidoreductase.

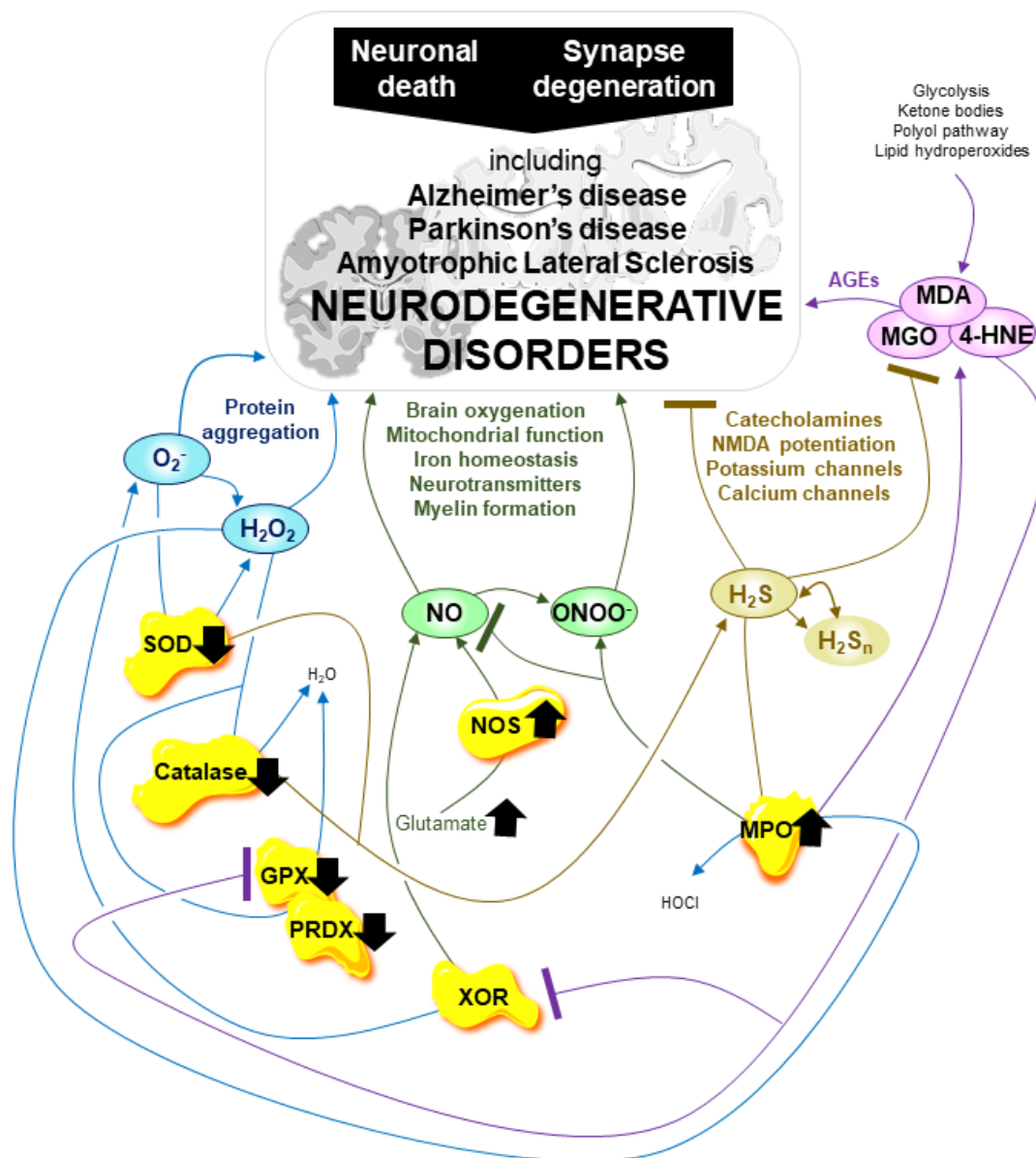


Figure 8. The RSI is a promising target for the treatment of neurodegenerative disorders. Oxidative distress mediated by RSS is beneficial in the fight against Alzheimer's disease, Parkinson's disease and Amyotrophic Lateral Sclerosis, while oxidative distress mediated by ROS, RNS, and RCS is detrimental. Moreover, key enzyme dysregulation, including SOD, catalase, XOR, MPO, GPXs, and PRDXs is detrimental. Circled reactive species are the known species involved in neurodegenerative disorders. AGEs, advanced glycation end products; GPX, glutathione peroxidase; MPO, myeloperoxidase; NMDA, N-methyl-D-aspartate; NOS, nitric oxide synthase; PRDX, peroxiredoxin; SOD, superoxide dismutase; XOR, xanthine oxidoreductase.

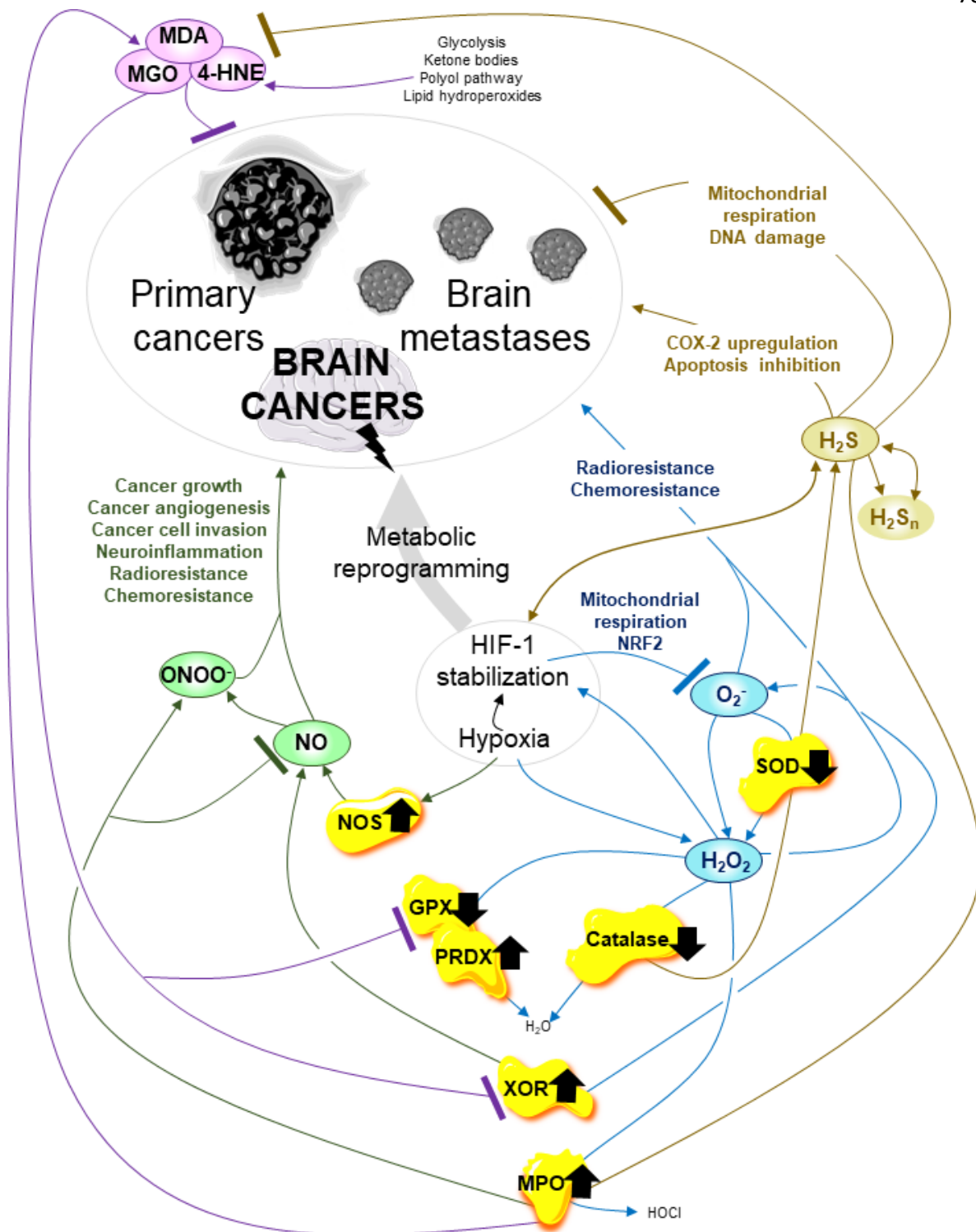


Figure 9. Notable reactive species and key enzymes in brain cancer. In primary tumors gliomas and brain metastases, the entire RSI is the ideal target through ROS, RNS, RSS, RCS, and key enzymes within. Associated with hypoxia status and response, oxidative distress mediated by RS is a promising anti-cancer therapy, while oxidative distress mediated by ROS, RNS, and RSS is pro-cancer. Key enzymes within the RSI have to be

considered, including SOD, catalase, MPO, XOR, GPXs and PRDXs. Targeting these enzymes is also a promising anti-cancer therapy, including in brain cancer. Circled reactive species are the known species involved in brain cancer. HIF-1, hypoxia-inducible factor 1; GPX, glutathione peroxidase; MPO, myeloperoxidase; NRF2, nuclear transcription erythroid-2-related factor 2; NOS, nitric oxide synthase; PRDX, peroxiredoxin; SOD, superoxide dismutase; XOR, xanthine oxidoreductase.

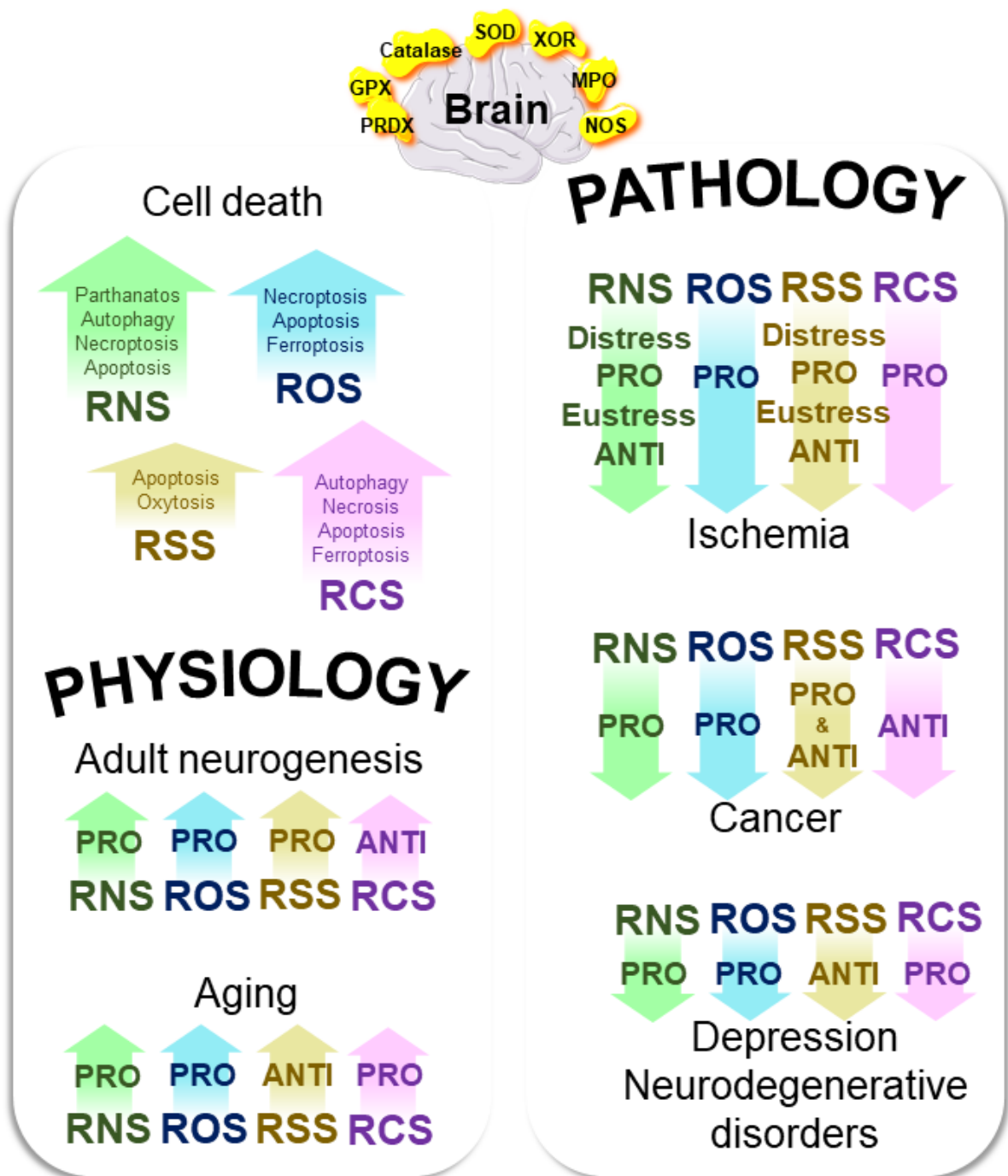
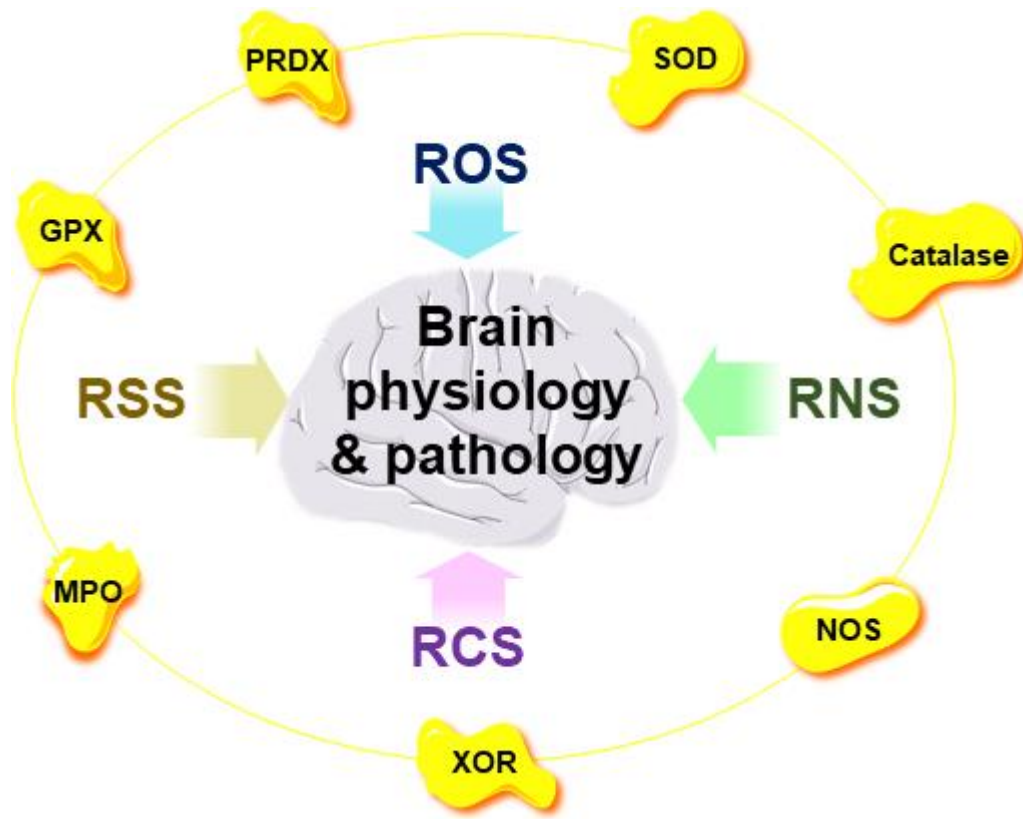


Figure 10. The reactive species interactome in brain physiology and pathology. The RSI, including RCS, is proposed as a nexus between the antioxidant defense and the bioenergetic metabolism that altogether display beneficial and detrimental roles in physiology and pathology. Key enzymes within the RSI, especially SOD, catalase, MPO, NOS, GPXs, PRDXs, and XOR, play essential roles in physiology and pathology, and have to be also investigated. The brain is a vital organ in which the RSI combined in eustress or distress is playing all its potential for mechanistic and therapeutic clues.



Graphical Abstract