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Executive (dys)Function after Stroke: Special Considerations for Behavioral Pharmacology

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Abstract

Stroke is a world-wide leading cause of death and long-term disability with concurrent secondary consequences that are largely comprised of mood dysfunction, as well as sensory, motor, and cognitive deficits. This review focuses on the cognitive deficits associated with stroke specific to executive dysfunction (including decision making, working memory, and cognitive flexibility) in humans, non-human primates, and additional animal models. Further, we review some of the cellular and molecular underpinnings of the individual components of executive dysfunction and their neuroanatomical substrates after stroke, with an emphasis on the changes that occur during biogenic monoamine neurotransmission. We concentrate primarily on changes in the catecholaminergic (dopaminergic and noradrenergic) and serotonergic systems at the levels of neurotransmitter synthesis, distribution, re-uptake, and degradation. We also discuss potential secondary stroke-related behavioral deficits (specifically, post-stroke depression as well as drug-abuse potential and addiction) and their relationship with stroke-induced deficits in executive function, an especially important consideration given that the average age of the human stroke population is decreasing. In the final sections, we address pharmacological considerations for the treatment of ischemia and the subsequent functional impairment, as well as current limitations in the field of stroke and executive function research.

Keywords

stroke; decision making; working memory; cognitive flexibility; monoamine; human

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Introduction

Afflicting nearly 795,000 people per year and associated with an annual cost of 34 billion dollars in the United States alone, stroke is the fifth leading cause of death and the leading cause of long-term disability (Benjamin et al., 2017). Importantly, direct costs associated with stroke patients' medical care are expected to triple in the coming decades as the "Baby Boomer" population ages (Heidenreich et al., 2011; Lesniak et al., 2008). The functional consequences of stroke can be diverse, and the success of medical recanulization interventions to re-establish blood flow and tissue oxygenation, such as chemical or mechanical endovascular therapy, are important predictors of outcome (Gurman et al., 2015; Rangel-Castilla et al., 2016). Currently, there is a paucity of pharmacological treatment options for stroke, despite many decades of research and many failed clinical trials of neuroprotective agents. The sole proven therapy for ischemic stroke is the thrombolytic agent recombinant tissue plasminogen activator (tPA), which can only serve limited patient populations and has an exceptionally short therapeutic window of 4.5-hours (Huang et al., 2006) due to the unacceptable increased risk of cerebral hemorrhage when given after that time point. Despite reductions in "door-to-needle" times in recent years, only a small fraction of stroke patients receive this intervention (Schwamm et al., 2013). Taken together, the large numbers of affected patients, the devastating long-term consequences of the disease, and the lack of viable treatment options highlight a critical need to characterize the neuropathological cascades associated with stroke and develop novel therapeutic interventions for the treatment of ischemia, its comorbidities, its secondary consequences and its long-term chronic symptoms.

Accounting for 87% of stroke cases, ischemic stroke is caused by blockage of a cerebral artery, resulting in a loss of blood flow to the brain area supplied by that artery; stroke due to other causes, such as intracerebral or subarachnoid hemorrhage, account for 10 and 3% of cases, respectively (Benjamin et al., 2017). Stroke represents a complex disease pathology that is profoundly influenced by a variety of factors including the ischemic or hemorrhagic nature of the stroke, localization of the infarct, as well as whether reperfusion was achieved and how quickly it took place following the insult (Bramlett & Dietrich, 2004). At the cellular level, ischemic stroke results in severe reductions in cerebral blood flow at the ischemic site, depriving neurons of crucially needed oxygen and glucose, which results in the depletion of adenosine triphosphate (ATP) reserves and an energy crisis in local brain tissues. Ionic disruption, metabolic stress, and cell death in this ischemic core are evident within hours of initial insult. Surrounding the necrotic core is the ischemic penumbra, in which tissues experience secondary impacts of stroke-induced pathological cascades affecting the core; this region represents an area at which therapeutic neuroprotective interventions can be directed. More broadly within the ischemic brain, stroke induces damage to white matter tracks, disruption of cerebrovascular integrity, and initiation of inflammatory pathways resulting in a series of long-term secondary brain injuries and numerous behavioral deficits. Generally, available interventions only target one facet of the heterogeneous injury cascade indicating a need to explore additional avenues for novel therapeutic targets that can affect multiple injury mechanisms and pathological cellular cascades, and ultimately ameliorate chronic symptomology to improve functional recovery.

Stroke Models

In order to adequately study the pathophysiology of stroke, as well as the effects of potential neuroprotective agents, selection of the appropriate animal model is necessary. Models of cerebral infarct have been assessed in a variety of species, including but not limited to rodents, rabbits, pigs, sheep, dogs, and non-human primates (NHP) (for reviews, see Bacigaluppi et al., 2010; Tajiri et al., 2013). For the purposes of this review, we will focus on the strengths and limitations of rodent and NHP animal models in experimental stroke research.

As described in the previous section, strokes can be broadly defined as either ischemic (a vessel blockage) or hemorrhagic (a vessel bleed), with cerebral ischemia being further dichotomized into focal (in which a singular vessel is occluded) and global (in which there is an overall lack of oxygen and nutrient substrates to meet the energy demands of the brain) subtypes. Both ischemic and hemorrhagic stroke have the capacity to impact different brain regions (e.g., cortical regions such as the frontal and temporal lobes, and subcortical regions such as the striatum, cerebellum, and brain stem, etc.) as well as different sections of prominent cerebral vasculature. Because of this inherent variability, factors such as lesion/infarct size and location, as well as cerebral blood flow, and sympathetic innervation leakage will also vary among stroke types. As such, various animal models have been developed to address the anatomical and physiological differences and their subsequent pathophysiological manifestations (Howells et al., 2010; Yan et al., 2015). In addition to the development of different types of stroke models, another factor to consider is variation within individual models. For example, certain types of stroke inductions can be either permanent or transient, with permanent models translating to an irreversible blockage of a vessel, and transient models allowing for the reversal of the blocked vessel via a procedure termed recanalization in which the occluded vessel is re-opened, often (but not always) followed by reperfusion, or the restoration of cerebral blood flow to the occluded site (Wells et al., 2012). As well, different techniques can exist to achieve the same parameters of a given model (Engel et al., 2011; Tamura et al., 1979), as we will discuss in this section.

The most common type of animal stroke model is that of focal ischemia. One approach to induce this pathology is through mechanical middle cerebral artery (MCA) occlusion (MCAO). Mechanical MCAO can be achieved through the use of intraluminal filaments or ligation sutures, surgical clips, or cauterization of the vessel through electrocoagulation (Engel et al., 2011; Howells et al., 2010; Tamura et al., 1979; Tyson et al., 1984; Yan et al., 2015). Some mechanical MCAO techniques, particularly the filament and ligation variations, can both be completed with (through either craniotomy or craniectomy) or without opening the skull (Agarwalla et al., 2014; Longa et al., 1989). Advantages of avoiding opening the skull include bypassing surgically-induced damage to the surrounding dura and cranial bone structures, as well as the possibility of cerebral spinal fluid (CSF) leakage. Also, standard MCAO models are often highly successful in stroke induction when performed by a skilled surgeon, with fairly low mortality rates (approximately 10%) (Wang et al., 2017), and can be achieved in several other species in addition to rodents and NHPs (Howells et al., 2010; Yan et al., 2015). However, some known disadvantages of mechanical MCAO include high variability of lesion/infarct volume and an inability to assess thromboembolism, a

characteristic of stroke pathophysiology commonly found in the human population (Howells et al., 2010). Furthermore, in MCAO models in which a craniotomy or craniectomy is not performed, but rather occlusion of the MCA is achieved via ligation through an incision made into the neck, there is the added concern of an induced pro-inflammatory response as a result of the surgical incision (in addition to the known, stroke-induced immune response) which may impact infarct pathophysiology, and as such, is not representative of human stroke. Moreover, non-mechanical techniques also exist for MCAO models and are primarily thrombo-embolic in nature, and have the advantage over MCAO models in that they more closely model human stroke. In brief, the traditional thrombotic model is accomplished via the injection of a clot-forming agent into the blood circulation near the MCA (Chen et al., 2015). Whereas the photothrombotic model incorporates the injection of a photo-sensitive dye to chemically induce thrombosis in a non-invasive manner (Watson et al., 1985). Other approaches can also be used to induce focal ischemia in rodents and NHPs. For example, a model that incorporates the injection of endothelin-1, a potent vasoconstrictor, and another model that implements the insertion and inflation of a catheter-guided balloon near the MCA, both achieve focal ischemia (Gao et al., 2006; Virley et al., 2003).

Applied less extensively in experimental stroke research are models of global ischemia. These models usually consist of quantifiable variations of vessel occlusion (VO). As such, the 2-, 3-, and 4-VO models are achieved through ligation of different combinations of the carotid, vertebral, and basilar arteries (Cechetti et al., 2010; Traystman et al., 2003; Yang et al., 2014). Induction of controlled cardiac arrest and subsequent resuscitation has also been implemented as a model of global ischemia (Kawai et al., 1992).

Although the majority of cerebral strokes are focal ischemia, researchers can also model hemorrhagic phenotypes. More specifically, two prominent subtypes of hemorrhagic stroke exist: intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). ICH occurs when weakened blood vessels rupture and leak into brain parenchyma. Common models of ICH include collagenase injection and balloon insertion and inflation (MacLellan et al., 2010; Sinar et al., 1987). Moreover, transgenic modification of rodent models has been used to create hypertensive mice that are highly susceptible to ICH with supplementation of a high-sodium diet (Alharbi et al., 2016); however, this model is not as easily accessible in NHPs as it is in rodents, as transgenic modification among NHPs raises extreme ethical, technical, and financial concerns. SAH occurs when ruptured blood vessels bleed “around” the brain, into the subarachnoid space, rather than “into” the brain as with ICH. Although less common in the human population than ICH, SAH models have also been validated across multiple animal species (Marbacher, 2016). A fairly reproducible model of SAH is performed through autologous blood injection; in this model, the blood is injected into the cisterna magna, a prominent opening within the subarachnoid space (Mori, 2014). Another common approach for SAH induction involves endovascular puncture of a subarachnoid vessel (Kooijman et al., 2014). An advantage of the endovascular puncture model over the autologous blood injection model, is that the mechanical and physiological damage surrounding the vessel injury can be easily studied and assessed.

In addition to examining the differences and similarities, as well as advantages and disadvantages among different models from a technical perspective, it is also critical to

consider the species to which a stroke induction model will be applied. A vast array of advantages and disadvantages exist between small animal models, such as rodents, and larger animal models, such as NHPs (Cook & Tymianski, 2012). For instance, advantages of rodent models over NHPs include an easier rate of replicability, lower variability of lesion size, an easier conduit for the implementation of genetic manipulation and intervention, an easier means of care, and a lower cost burden (Cai & Wang, 2016). In contrast, broad physiological, immunological, and behavioral differences between rodents and NHPs exist, with NHPs proving much more analogous to humans than rodents (Cai & Wang, 2016; Fan et al., 2017; Jickling & Sharp, 2015; Mestas & Hughes, 2004; Phillips et al., 2014). Similarly, various aspects of brain anatomy, including cerebral volume, white matter-to-gray matter proportion, cerebral vasculature, and whole brain complexity (a more complex, gyrencephalic NHP brain compared to a lissencephalic rodent brain) also demonstrate the advantage of using an NHP model over a rodent model (Cai & Wang; Fan et al., 2017). Moreover, with NHPs having more anatomically similar brain regions to humans than rodents, it is easier to map on the functions and behavioral outcomes of a more developed, NHP prefrontal cortex (PFC), the brain region responsible for executive functioning, to the human PFC. Taken together, these anatomical similarities between humans and NHPs are intricately linked to their functional outputs, and as such, could allow for a much stronger assessment of executive function in the human stroke population.

Stroke and Executive Dysfunction

One area of deficit that has the potential to exert profoundly negative impacts to quality of life among stroke survivors is that of executive function. Below, we review executive-function deficits following stroke in humans, non-human primates, and additional animal models. Further, we review some of the cellular and molecular underpinnings of the individual components of executive dysfunction after stroke, with an emphasis on the changes that occur in biogenic monoamine transmission due to the importance of this system in executive functioning (for reviews, see (Arnsten & Li, 2005; Logue & Gould, 2014; Robbins & Arnsten, 2009), particularly changes in the catecholaminergic (dopaminergic and norepinephrine) and serotonergic systems. It is worth noting that currently there is insufficient literature evaluating the changes of various endogenous monoamine neurotransmitter systems during executive dysfunction in the context of stroke. Rather, the literature is divided into three bodies: one that focuses predominantly on monoamine neurotransmission modulation during executive function/dysfunction, one that addresses executive dysfunction associated with stroke, and one that emphasizes monoamine neurotransmission disruption following stroke. Thus, we draw from multiple bodies of primary literature in an attempt to bridge the gaps between these three bodies of literature, thereby more precisely elucidating potential therapeutic avenues for the treatment of monoamine neurotransmission-induced executive dysfunction in the stroke population.

Secondary consequences of stroke are largely comprised of mood dysfunction, as well as sensory, motor, and cognitive deficits. This section of the review will focus on the cognitive deficits associated with stroke, specifically those associated with executive dysfunction that frequently afflict post-stroke patients. Executive dysfunction occurs in as much as 75% of stroke patients and poses a critical problem for the quality of life of these individuals

(Lesniak et al., 2008; Riepe, Riss, Bittner, & Huber, 2004; Zinn, Bosworth, Hoenig, & Swartzwelder, 2007). From both a human and non-human perspective, we can model executive function as an assemblage of multiple components primarily comprised of the following cognitive processes: inhibitory control, which is closely related to impulsivity, the ability to plan and make decisions, working memory, and cognitive flexibility, which is associated with mental speed processing, problem solving/error processing, and attentional control (Diamond, 2013); these processes are largely carried out in the PFC of the mammalian brain (Squire, 2013). However, it is important to note that many of these components are not necessarily independent, often working in concert with one another to accomplish top-down, goal-driven tasks (for example, maintaining attention control, and therefore utilizing the inhibitory response to block irrelevant stimuli, is necessary for intact working memory during problem solving and reasoning tasks), as we will address below. Further, within both pre-clinical and clinical settings, executive function can be assessed either through laboratory-based or naturalistic/real-world situations (Chan et al., 2008). Among the stroke population, it is common for one or more neurotransmitter systems to be altered as a downstream result of the ischemic or hemorrhagic insult (Kanthan et al., 1996; Weinberger & Nieves-Rosa, 1988; Wurtman & Zervas, 1974), potentially leading to poor long-term cognitive outcomes in which patients struggle with high-level intellectual functioning and additional behavioral sequela (e.g., drug-abuse potential or drug-seeking behavior, an area in which evidence is currently lacking and in further need of research, as well as post-stroke depression), which will be discussed later in this review.

Impulsivity (Decision-Making/Risk-taking/Planning/Inhibitory control)

Decision-oriented impulsivity is defined as a behavioral response that is often the result of rapid decision making with little to no pre-meditated consideration of the consequences that may arise from the decision or behavior and is generally mediated by the medial orbitofrontal cortex (mOFC) in humans (Bechara et al., 2000a). The impulsivity construct can also be motor-oriented. Indeed, motor impulsivity is generally described as a failure to implement the inhibition control response (Roharikova, 2016) and is maintained primarily by the fronto-basal-ganglia network (Chamberlain & Sahakian, 2007). Individuals displaying impulsive tendencies struggle with the ability to plan and lack inhibitory control, often leading to risky decision-making in potentially harmful situations (reviewed in (Jurado & Rosselli, 2007). In humans, multiple studies have documented that post-stroke individuals often struggle with impulsivity and decision making (Bechara et al., 2000b; Binder, 1984; Poulin et al., 2013). For example, Scheffer and colleagues (2016) used the Go/No-Go motor-impulsivity task to show that patients with right frontal-lobe stroke performed worse than the control group. In the Go/No-Go task, an individual is asked to perform a specific action in response to a specific stimulus (‘Go’) and to inhibit that same action in response to a different stimulus (‘No-Go’) (Gomez et al., 2007)., Cardoso et al. (2014) implemented the Iowa Gambling Task as a measure of both risky decision making and impulsivity to frontal-lobe and cerebellar-lobe stroke patients and healthy controls. During The Iowa Gambling Task, participants must choose cards from decks that are either associated with a ‘reward’ or a ‘penalty’. Individuals with inhibitory control and decision-making deficits will often impulsively choose cards that are associated with a penalty even after a reward versus penalty distribution pattern has been established (Buelow & Suhr, 2009). Both stroke groups

performed poorly relative to the healthy participants, and when compared to each other, the two stroke groups did not significantly differ in their performances (Cardoso, 2014), suggesting that the PFC is not the only region responsible for governing executive function, at least in the context of stroke.

Working Memory

Working memory is an active form of short-term memory that is able to be manipulated via attention shifting, blocking of external, irrelevant stimuli, and updating of the contents being held in the working memory in order to achieve problem solving tasks (Squire, 2013) and is processed primarily within the dorsolateral PFC (Levy & Goldman-Rakic, 2000). Working memory typically lasts within the broad range of a few seconds to several hours, and can be categorized into two primary subtypes—verbal and spatial—both of which can be assessed through stimulus-specific behavioral tasks. Like most components of executive functions, an intact working memory involves the utilization of other functional components. For example, a deficit in working memory would likely impede one's ability to plan, as the individual would display difficulty in retaining the relevant information for an abbreviated time window. Also, certain behavioral measures of impulsivity are associated with working memory deficits in rodent models (James et al., 2007).

Human studies have indicated working memory deficits in the stroke population. For example, van Geldorp and colleagues (2013) used a computerized delayed-match-to-sample task in which participants were shown either spatial, object, or binding (spatial + object) cues and then had to remember which cue was presented after a brief temporal delay. Relative to controls, stroke patients showed working memory deficits on both spatial and object-based components of the task, but not the binding component, suggesting that different neuroanatomical regions are implicated in the subdimensions of working memory. Further, Roussel et al. (2012) investigated the impact of stroke on both the visuospatial and verbal components of working memory. In their study, stroke patients were assessed on phonological loop (verbal working memory), visuospatial sketchpad (visuospatial working memory), and central executive (the "master" integrator between the two sub-systems). The results indicated mild working memory impairment in stroke patients with frontal lobe lesions, with an emphasis on the rehearsal process aspect of the phonological loop component of verbal assessments, and less discernible deficits in the spatial components of the working memory-based tasks. Roussel and colleagues (2012) attributed these discrepant findings to regional differences in patients with frontal versus posterior lesions.

In alignment with the association between the cerebellar region and impulsivity-based tasks (Cardoso et al., (2014), this region has also been implicated during working memory procedures. As such, functional magnetic resonance imaging (fMRI) studies have shown the importance of the cerebellum, specifically the cortico-cerebellar circuitry, for intact working memory. Specifically, Ziemus et al. (2007) used fMRI during a computerized 2-back working memory assessment, in which participants had to remember a specific sequence of presented letters on a computer screen in such a way that whenever the current letter presented was the same as the letter presented the one before the last (or '2-back'), they made a response. Results demonstrated that stroke patients with cerebellar lesions had

increased activation in posterior and cerebellar regions relative to healthy controls, who had activations in all regions of the cortico-cerebellar circuitry; this suggested a possible compensatory mechanism among stroke patients in which the cerebellum was utilized during the working memory task.

In addition to evidence from human studies, researchers have demonstrated the impact of ischemic infarct on memory using murine models. Specifically, Zhou et al. (2016) implemented a photothrombosis model of focal stroke in the PFC, such that post-stroke regional connectivity and certain behavioral outcomes (i.e., working memory) could be assessed. Post-stroke, mice were tested on an object location recognition task in which animals were allowed to explore two identical objects in an empty arena. After a delay interval, one of the original two objects was moved to a new location in the animal. Object preference was used as the primary dependent variable, as mice with intact memory can discriminate the novel location better than mice with memory deficits (Dix & Aggleton, 1999; Vogel-Ciernia & Wood, 2014). Both the stroke and sham mice were able to discriminate the novel location at one week post-stroke, but only sham mice were able to discriminate novelty four weeks post-stroke, indicating a delayed-onset spatial memory deficit in PFC stroke mice (Zhou et al., 2016).

Cognitive Flexibility (Speed and Error Processing/Attention)

Cognitive flexibility is defined as an ability to shift or update mental processes depending on changing stimuli in the environment, and is processed predominately in the ventrolateral PFC (Verdejo-Garcia et al., 2015). Like most other components of executive function, this component relies heavily on the simultaneous interplay of various other processes, such as attentional control, speed and error processing, working memory, and inhibitory control (for review, see (Diamond, 2013). For example, the ability to teach or learn a new concept using different methods involves the utilization of different thought perspectives via the inhibition of one perspective and the adaptation of a new perspective, a cornerstone of cognitive flexibility. Furthermore, cognitive flexibility is essential for higher-level executive functioning such as problem solving, reasoning, and abstract thinking, and is thus seen as a crucial component to fluid intelligence (Dajani & Uddin, 2015; Ionescu, 2012).

Deficits in attentional control, or ‘set-shifting’, can be seen post-stroke through the implementation of the Wisconsin Card Sorting Test (WCST), a test that requires participants to match or classify cards based on instructions given by the experimenter (i.e., match the cards according to number, color, shape, etc.). Once participants establish a correct pattern of matching, they are reinforced only when they adapt a new matching strategy, thus shifting them from one processing strategy to another (Mountain, 1993; Nyhus & Barcelo, 2009). Neurologically healthy individuals with no PFC impairment should be able to shift and update card-matching strategies fairly easily, while those with attentional control deficits will likely be unable to adjust their cognitive strategy and will instead perseverate on the original method. Su et al. (2008) implemented a variation of the WCST (WSCT-64) with stroke patients and found that it was a sensitive assessment for detecting deficits in cognitive flexibility in such a population. However, other researchers have disagreed (Jodzio & Biechowska, 2010) due to the lack of executive function-related factors assessed and

therefore overly broad evaluation, resulting in some discrepancy in the field. Taken together, the conflicting reports of the validity of the WCST among the stroke population should warrant caution among clinicians when choosing the appropriate tools for post-stroke assessment.

Given that thalamic and sub-thalamic regions have neuronal projections to the frontal lobe (Cardoso, 2014), a study by Cordova and colleagues (2014) addressed the impact of rodent stroke-induced thalamic and medial PFC infarcts on an attentional set-shifting task. Rats were trained to find a buried food reward prior to task administration. During the first day of the task, rats were rewarded for responding to a stimulus associated with one of the possible locations of the buried reward. On subsequent days, rats had to discriminate between relevant and irrelevant stimuli associated with the food reward, followed by new locations of buried food associated with a new stimulus; this required the rats to shift their attention from a previously learned association between stimulus and food reward to a new association for a rewarding stimulus. Rats with medial PFC-based strokes performed worse than their thalamic-based stroke and control counterparts. Moreover, no deficits in attentional set-shifting in thalamic-lesioned rats were observed, thus emphasizing the importance of stroke region specificity in executive dysfunction.

In addition to the importance of regional specificity, age may be a vital factor in determining deficits in post-stroke cognitive flexibility. Indeed, it is known that general age-related processes have negative impacts on cognitive flexibility; however, this effect could be potentiated by additional post-stroke pathophysiology. Furthermore, although there are broad similarities among the pathophysiological processes of stroke-induced brain injury in varying ages of stroke populations, age-related differences still exist. As such, Cipolotti et al. (2015) reported cognitive differences related to aging among stroke patients in terms of the Stroop test of attention control, speed, and error processing. For the Stroop test, individuals must read a word aloud, often a color name, which is printed in a contrasting color (i.e., reading the word ‘green’ with all of the letters in the word green being printed in the color red) (Jensen & Rohwer, 1966; Scarpina & Tagini, 2017). Cipolotti and colleagues (2015) determined that age exacerbated executive dysfunction among stroke patients, suggesting that deficits in cognitive flexibility following stroke are likely due to a multitude of variables, including age.

Monoamine Neurotransmission Disruption Following Stroke

Decision-making, working memory, and cognitive flexibility are associated with modulation of the monoamines – dopamine, norepinephrine, and serotonin. Dopamine (DA), is synthesized primarily in the substantia nigra and ventral tegmental areas (VTA) with clearly defined cortico-limbic pathways implicated in its neurotransmission (Squire, 2013). Serotonin (5-HT) is produced in the raphe nuclei of the brain stem and is transported through extensive pathways before exerting its cognitive effects within the PFC (Squire, 2013). Norepinephrine (NE) is synthesized in the brainstem locus coeruleus and exchanges information with the PFC via well-established cortico-cerebellar connections (Campbell et al., 2008; Paterson et al., 2012; Squire, 2013). Biogenic monoaminergic disruption is a consequence of ischemic and hemorrhagic strokes (Kanthan et al., 1996; Weinberger &

Nieves-Rosa, 1988; Wurtman & Zervas, 1974), leading to deficits in various executive-function components. Further, the disruptions due to brain insult in both subcortical and cortical regions result in attenuated neurotransmission of the various monoamine projections to the PFC, where they exert their primary influence, as well as excitotoxicity. As such, upon ischemic or hemorrhagic cerebral insult, the 'leaking' of these monoaminergic neurons and axons into the extracellular spaces consequently exacerbates the pathophysiological changes caused by the initial insult, leading to further death of surrounding neurons. Below we will address the different mechanisms during monoaminergic signaling processes by which neurotransmission can be impacted following stroke.

Biosynthesis Enzymes and Monoamine Precursors

Monoaminergic precursors and the biosynthesis enzymes with which they interact in order to synthesize and secrete neurotransmitters are crucial to normal neuronal functioning. Here, we will address these precursors and related enzymes for the catecholaminergic and serotonergic systems. Tyrosine hydroxylase (TH) is the biosynthesis enzyme responsible for the conversion of L-tyrosine to L-3,4,-dihydroxyphenylalanine (L-DOPA), the direct precursor of dopamine. Stroke literature has suggested that TH plays an important role in the disease pathophysiology. As such, Huh and colleagues (2003) demonstrated a link between transient changes in dopaminergic, TH-positive neurons and microglial activation in a rat stroke model, wherein a marked reduction of TH positive dopaminergic cells was observed in the substantia nigra pars compacta 7 days post insult, but only on the lesioned side of the brain; this effect was associated with a biphasic microglia activation response. A similar trend of reduced TH-positive dopaminergic cells within the ipsilateral side relative to the contralateral side 7–14 days post-stroke was observed in a previous study by (Soriano et al., 1997).

DA beta hydroxylase (DBH) is a membrane-bound biosynthesis enzyme responsible for the conversion of DA to NE and has been utilized as both a biomarker and target for pharmacological manipulation within the catecholaminergic systems (Kaufman & Friedman, 1965; Rush & Geffen, 1980). Upon ischemic or hemorrhagic insult, NE levels within the PFC drastically decrease as noradrenaline leaks from neurons into the surrounding vasculature. This consequent reduction in brain NE can be translated to increased DBH in the peripheral blood serum, as blood-brain barrier (BBB) permeability increases after stroke (ElAli et al., 2011; Merali et al., 2017), and could possibly be the result of a compensatory measure. As such, Kanda and colleagues (1979) first demonstrated this post-stroke consequence when they sampled serum DBH in stroke patients at multiple time-points after the initial insult, finding the highest levels of DBH immediately after stroke, with the values gradually declining in a time-dependent manner.

More recently, another study examined the levels of tryptophan (5-HT precursor), tyrosine (DA/NE precursor), and their metabolites among stroke patients. Ormstad et al. (2013), found decreased plasma levels of the monoamine precursors in stroke patients relative to healthy controls. This decrease in monoamine biomarkers relative to the increase in DBH shown by Kanda et al. could possibly be attributed to differences in blood collection time-points utilized. Ormstad and colleagues attributed reduced levels of monoamine precursors

to increased oxidation of tryptophan and tyrosine in the stroke group, a finding which supports the notion of an increased release of reactive oxygen species during the acute phase of the post-stroke signaling cascade (Crack & Taylor, 2005; Olmez & Ozyurt, 2012).

Neurotransmitters, Receptors, and Transporters

Depending on the location and severity of the infarct, changes in certain neurotransmitter levels occur at various time-points following the initial ischemic insult. These time-dependent changes affect monoamine receptor- and transporter-binding densities, and consequently, neurotransmission and cognition (Brouns et al., 2010; Weinberger & Nieves-Rosa, 1988). For example, a study by Tsukada and colleagues (2004) revealed changes in both DA and 5HT levels and receptor binding in a monkey stroke model. Specifically, positron emission tomography (PET) and microdialysis techniques revealed hyperactivation of the cyclic adenosine 3', 5'-monophosphate (cAMP) second messenger system, via modulation of specific 5-HTergic and DAergic receptor systems post-experimental stroke in non-human primates. Upon further probing of these systems, radioligand binding and PET analyses revealed decreased D1 and 5-HT_{1A} receptor binding 7 days post-insult. Microdialysis showed transiently increased striatal DA levels during both the occlusion and reperfusion phases of ischemia; in contrast, 5-HT levels increased transiently only after reperfusion had occurred (Tsukada et al., 2004). Taken together, these findings indicate that cAMP activation modulated by specific dopamine and serotonin receptor systems could contribute to monoaminergic neuronal death post-stroke.

The DA transporter (DAT) has also been implicated in post-stroke monoamine alterations. A study by Momosaki et al. (2017) assessed both DA receptor and transporter expression in the rat brain following mild ischemia. Results showed time-dependent expression of receptor and transporter levels that corresponded to a presence or absence of circling behavior, a specific type of post-stroke locomotor behavioral deficit in which the animal is unable to walk in a straight line and will often walk in a circular pattern. Specifically, PET and radioligand binding analysis revealed a transient increase in DAT at two days post-stroke, with decreased receptor binding levels observed at 7–14 days post-stroke. An increase in circling behavior also appeared at 14 days after insult. In addition to alterations in DAT, Mortensen and colleagues (2018) analyzed the 5-HT transporter (*SERT*) gene for its role in the relationship between platelet aggregation and ischemia. SERT provides the mechanism by which platelets uptake 5-HT and it has been implicated in myocardial ischemia (Coto et al., 2003); the study of Mortensen et al. (2018) revealed that polymorphism-associated genotypes of the *SERT* gene (a high expression SERT genotype) may be associated with a reduced risk of cerebral ischemia.

The expression of NE receptors in stroke patients has also provided insight into the progression of stroke pathology and potential treatment. A study by Tsukahara and colleagues (1988) first characterized the role and expression of the alpha-adrenergic receptor in subarachnoid-hemorrhage stroke patients using radioligand-binding assays. These seminal findings revealed a reduction of high-affinity alpha-adrenergic receptors in the stroke group that was likely caused by sympathetic denervation of NE-containing neurons upon hemorrhagic insult. Furthermore, this denervation was responsible for the increase of NE

levels in cerebral arteries and likely contributed to the physiological secondary stroke process of vasospasm, or a spasm of cerebral arteries leading to vasoconstriction and neuronal death in the acute post-stroke phase.

Immune-response signaling cascades after stroke have also been shown to impact cognitive ability (Becker et al., 2016; Doyle et al., 2015). It has been recently shown that the converging interaction between the monoaminergic and immune systems post-cerebral insult plays in important role in both infarct evolution and the development of therapeutic intervention. This interaction was elucidated in a study by Huck et al. (2015), in which the authors showed modulation of the immune response via DA receptor signaling after stroke. In the study, a mouse stroke model was used to quantify DA receptor expression in stroke animals relative to controls. Interestingly, the authors noted *de novo* expression of the DA receptor, D2, on activated microglia in both the infarct and penumbra regions of the mouse brain, in the stroke group relative to the control group. The high expression of D2 receptors was additionally identified in the peripheral macrophages of the stroke animals. This crucial finding suggests a possible role for therapeutic targeting of DAergic receptors as immune modulators in stroke patients.

Degradation Enzymes and Metabolites

Degradation enzymes are key in the maintenance of monoaminergic metabolism and homeostasis. Indeed, alterations in monoaminergic degradation enzymes have also been implicated in stroke secondary pathology. The degradation enzyme, catechol-*O*-methyltransferase (COMT), is crucial for maintenance of both DA and NE metabolism in the brain (Huotari et al., 2002; Kaenmaki et al., 2010). A study by Kim and colleagues (2016) examined the relationship between *COMT* gene polymorphisms and stroke functional recovery. They found that *COMT*-specific polymorphisms were associated with an ability to predict motor recovery in stroke patients in a time-dependent manner. Additionally, monoamine oxidases (MAO), degradation enzymes located within the mitochondrial cell walls of pre-synaptic neurons that are responsible for the break-down of 5-HT, DA, and NE into their respective metabolites, 5-hydroxyindoleacetic acid (5HIAA), 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 3-methoxytramine (3-MT), 3,4-dihydroxymandelic acid (DHMA), and 3-methoxy-4-hydroxyphenylglycol (MHPG), are also implicated in post-stroke outcomes. As such, studies have evaluated the isolation of these monoaminergic metabolites post-stroke and found increased concentrations in CSF using high-performance liquid chromatography (HPLC) (Tang et al., 1989; Wester et al., 1987). Additional work by Uzbekov et al. (2011) analyzed blood samples from ischemic stroke patients and found increased MAO activity in stroke platelet samples several days after the initial ischemic insult. They suggested that this effect could be a compensatory mechanism to re-establish brain tissue homeostasis, as an increase in stroke monoamine activity is likely due to an increase in monoamine deamination activation and subsequent glutamate-induced excitotoxicity.

Behavioral Sequela Secondary to Stroke-Related Executive Dysfunction

Post-Stroke Depression

Post-stroke depression (PSD) affects at least one-third of stroke patients (Santos et al., 2009) and has become of crucial importance within the biomedical field. Symptomatically, patients with PSD often present with many of the same afflictions as patients with major depressive disorder (MDD), in particular, executive-function impairment. Moreover, the relevance of PSD to executive function has been thoroughly studied (Nilsson, 2016; Nunes, 2012; Pohjasvaara et al., 2002; Sobreiro et al., 2014), and at present, has far-reaching implications for public health (Amaricai & Poenaru, 2016). Indeed, commonly impacted components of executive function among PSD individuals are working memory and specific components of cognitive flexibility, such as attentional control (Nilsson, 2016; Nunes, 2012; Pohjasvaara et al., 2002). A prospective study by Ilut et al. (2017) examined potential factors that could influence the severity of PSD. Both stroke-lesion location and the number of lesions were associated with severity levels of PSD, with patients diagnosed with left hemisphere and/or basal nuclei- or frontal lobe-located lesions suffering from significantly more severe PSD, and patients with a smaller number of lesions (e.g., 1–2) being more likely to develop mild-to-moderate PSD than patients with a great number of lesions (e.g., 3–4). As well, Sibolt et al. (2013) showed that PSD is more likely to occur in patients with recurring stroke episodes. Moreover, as with MDD, women are more likely to develop PSD than men (Appelros et al., 2010).

It is known that dysregulation of monoaminergic neurotransmitter systems plays a role in PSD. As such, it has been hypothesized that the monoamine theory, in part, characterizes the biochemical underpinnings of PSD, wherein levels of the key biogenic monoamines involved in executive functioning—5-HT, DA, and NE—have reduced bioavailability in various regions of the PFC (for reviews, see (Feng et al., 2014; Loubinoux et al., 2012). Evidence to support the monoamine theory of PSD has been demonstrated in numerous studies. For example, Gao and colleagues (2008) sampled stroke survivors diagnosed with PSD and found that, relative to healthy controls, PSD patients had significantly lower levels of plasma and CSF 5-HT. Further evidence supporting the decrease of 5-HT levels among PSD patients was reported in a study by Ramasubbu et al. (2008), which examined the genetic make-up of stroke patients with PSD and found a relationship between a single nucleotide polymorphism (SNP) encoding for a SERT gene and an increased risk of developing PSD after stroke. Specifically, Ramasubbu and colleagues (2008) implemented polymerase chain reaction genotyping to analyze a specific promotor region of the SERT gene, 5-HTTLPR/rs25531, among PSD and healthy controls, and found that PSD patients had lower occurring allelic frequencies of the SERT gene-promotor region relative to healthy individuals.

In addition to 5-HTergic system dysregulation, alterations of NE and DA neurotransmitter systems have also been implicated in PSD. For example, Ji and colleagues (2014) utilized HPLC to assess levels of 5-HT, NE, and DA in the PFC and hippocampus of a rat model of PSD. Levels of all three neurotransmitters were significantly diminished in the PSD group relative to the stroke group. The importance of DAergic neurotransmission in post-stroke

affect has also been elucidated in a human study by Delbari et al. (2011). Stroke patients were prospectively enrolled in the study during which they were administered the biochemical precursor of DA, Levodopa, and the DA reuptake inhibitor, methylphenidate, in combination with physiotherapy during the acute recovery phase post-stroke. Results showed significant improvements in mood and cognition in the Levodopa + methylphenidate group relative to a placebo control group, as measured by various mood, cognitive, and neurological assessments, with the most prominent effects observed in early follow-up time-points after pharmacological intervention. Moreover, disruption of biogenic monoamine neurotransmission in PSD can be correlated to behavioral changes in animal models. Specifically, Wu and colleagues (2015) showed increased immobility in the Forced Swim test, decreased mobility in the Open Field test, and decreased sucrose consumption in the Sucrose Preference test in a rat model of PSD, which are all indices of enhanced anxiety-like and depressive-like phenotypes in rodents.

Drug-Abuse Potential and Addiction

Although the literature supporting the topic is scant, one can hypothesize that, as the size of the stroke populations continue to grow and additional data are acquired, the possibility of post-stroke addiction could become a new reality. Currently, it is well established that particular components of executive function, such as impulsivity and decision making, are compromised in individuals suffering from addiction (see review, (Bickel et al., 2012). Also, much is already known about monoaminergic system disruption in addiction. Implications of DA in addiction have been well-established (Groman & Jentsch, 2012). 5-HTergic signaling in the mPFC and OFC has also been implicated in drug-abuse potential, indicated by significant effects of the 5-HT_{1A} receptor agonist, 8-OH-DPAT, in decreasing impulsive behavior on a delay-discounting task (London et al., 2000; Schoenbaum & Shaham, 2008; Yates et al., 2014). Moreover, these behavioral deficits are demonstrated in the human stroke population: patients with stroke lesions in the ventral mPFC opt for immediate gains over future, higher losses in a card gambling task. Further, their card choosing strategies showed poor decision making abilities and enhanced risk-taking behavior, which indicates a lack of awareness of future consequences (Bechara et al., 2000b). With an already established link between stroke and drug-abuse (de los Ríos la Rosa et al., 2012; Fonseca & Ferro, 2013), in which addiction is a known risk factor for stroke, more research is needed to determine if there is a similar relationship between addiction development post-stroke. Indeed, epidemiological studies have indicated that the average age of stroke is decreasing, concomitant with an increased prevalence of stroke in younger populations (Kissela et al., 2012; Smajlovic, 2015), conferring an increase in medical and financial burdens associated with executive function-related impairments in the younger population.

Given the overlap of executive dysfunction-related behavior, monoamine signaling disruption, and addiction among the adult stroke population, perhaps one overlooked population that could become susceptible to post-stroke executive function deficits that could drive subsequent drug-seeking behavior and addiction is that of neonatal and pediatric hypoxic-ischemic insult patients. Specifically, it is well-known that hypoxic-ischemic encephalopathy (HIE) is a debilitating condition whereby global ischemic insult due to oxygen deprivation before, during, or shortly after birth can impart devastating behavioral

and motor deficits long withstanding into adulthood (Douglas-Escobar & Weiss, 2015; Riljak et al., 2016). Although acknowledged as a diagnosis dissociable from adult stroke, it is understood that there is substantial pathophysiological parallel between HIE and stroke, as many of the same pro-inflammatory cascades and monoaminergic systems are altered within both forms of ischemic brain injury (Hama et al., 2017; Povroznik et al., 2018; Shiraishi et al., 2008; Wurtman & Zervas, 1974). Of these stroke and HIE-related deficits, and relevant to the present review, executive function profiles of children with HIE have been examined. A study by Hayes and colleagues (2018) found that, of the components of executive function assessed using the Behavior Rating Inventory of Executive Function, children less than 42 months of age who were diagnosed with HIE at birth showed attention- and working memory-related deficits relative to healthy controls. These findings can be correlated to a previous study by Decker et al., (2003), in which dopamine neurotransmission was disrupted in neonatal HIE rat pups, as it is known that dopaminergic signaling is key to attentional control and working memory function (Nieoullon, 2002; Shiner et al., 2015). Thus, it is possible that children who have experienced neonatal HIE represent an at-risk population for developing addiction later in life, a burden they will carry for many decades. That the literature specifically examining this issue is scant warrants more research in this component.

Pharmacological Considerations for Stroke in the Context of Executive Function

In light of the fact that tPA, aimed primarily at recanulization, is currently the only FDA-approved therapeutic intervention for ischemic stroke (Mozaffarian et al., 2015; Rouchaud et al., 2011), there is a crucial clinical need to develop additional interventions that can address the spectrum of long-term pathological consequences of stroke, including disruptions to executive function. Targeting the monoaminergic system may be a viable option as emerging evidence suggests positive impacts on functional recovery, especially in the domain of motoric ability (Chollet et al., 2014; Cramer, 2015). Indeed, beneficial findings of the FLAME trial, in which a selective 5-HT reuptake inhibitor (SSRI), fluoxetine, improved motor recovery among non-depressed stroke patients, indicate that monoamine-targeted treatments could represent a promising new intervention (Chollet et al., 2011). This is supported by collective findings of the recent Cochrane meta-analysis noting benefits primarily in motor and affective domains (Mead et al.t, 2013) as well as other small clinical trials in which other drugs targeting 5-HT were used to induce positive effects on post-stroke motor performance (Acler et al., 2009; Zittel et al., 2008).

Similar beneficial impacts on post-stroke outcomes have been reported with other monoamines. For example, physical therapy combined with L-DOPA treatment in post-stroke patients was associated with significantly greater motor improvement as compared to placebo treatment, an effect that persisted at least 3 weeks following the cessation of treatment (Scheidtmann et al., 2001). The results of the multi-center, randomized, double-blinded, placebo-controlled Dopamine Augmented Rehabilitation in Stroke (DARS) clinical trial (Bhakta et al., 2014), in which the L-DOPA medication, co-careldopa, will be evaluated for its potential to improve motor recovery, are eagerly anticipated. Administration of other

DA agonists has yielded beneficial impacts on functional recovery, improved somatosensory circuit remolding, attention, and mood (Obi et al., 2018; Sami & Faruqui, 2015).

Although a paucity of studies evaluating the impacts of noradrenergic modulation have been conducted to date, evidence is promising. Indeed, stroke patients treated with dextroamphetamine, a potent NE stimulator, showed improved motor recovery when paired with physical therapy, as compared to placebo-treated patients (Walker-Batson et al., 1995; but see Sprigg & Bath, 2009, for review of the accumulating evidence to suggest that amphetamines impair stroke recovery). In a pilot study, acute inhibition of the NE transporter with reboxetine resulted in improved motor recovery and partially restored neural circuit connectivity following stroke in human patients (Wang et al., 2011; Zittel et al., 2007). It has been hypothesized that targeting these systems induces benefits in the ischemic brain via their ability to modulate inhibitory signaling pathways, enhance long-term potentiation, facilitate neurogenesis, and promote neural plasticity (reviewed in (Chollet et al., 2014; Cramer, 2015; Feeney et al., 2004; Pinto et al., 2017; Siepmann et al., 2015).

Whether monoamine-targeted therapies will exert beneficial effects for domains of cognition and executive function in addition to locomotor ability remains to be thoroughly evaluated. Findings pointing to the monoaminergic system as a new therapeutic target for stroke are encouraging; however, not all studies have reported positive results. For example, the Cochrane meta-analysis noted no benefit of SSRI treatment in cognitive domains and the FLAME trial did not evaluate cognition at all (Chollet et al., 2011; Mead et al., 2013). Further, while several studies noted benefits of SSRI treatment post-ischemic stroke on motor recovery, pre-stroke or peri-stroke SSRI use was associated with increased hemorrhagic stroke severity and mortality (Miedema et al., 2010; Mortensen et al., 2014), highlighting the potential for stroke etiology and/or pre-morbid conditions such as depression to interact with the actions of SSRIs in the context of acute brain injury. Similarly treatment with DAergic system modulators such as the D2, D3 and D4 agonist, ropinirole, have not always shown beneficial effects (Cramer et al., 2009). This may be due to a receptor-specific effect as Okada and colleagues (2005) reported that antagonism of the D4 receptor attenuated stroke-induced cell damage in vitro. Finally, while others have shown that reductions in NE were associated with worse functional recovery (Beltran et al., 2010), Windle and colleagues (2007) noted beneficial effects of NE depletion on a variety of rodent tests of motoric ability. These collective findings suggest that the relationship between post-stroke recovery and monoaminergic-system modulation may be more complex than previously appreciated, presenting additional challenges in translating findings from rodents to humans, and implementing these interventions in the clinic. Future interventions may need to consider the targeting of multiple neurotransmitters and/or multiple levels of the monoaminergic systems.

More broadly, the current lack of viable neurorestorative interventions for stroke and the null or negative findings of recent clinical trials evaluating efficacy of novel interventions is disheartening and has warranted careful scrutiny among scientists and clinicians of the causes for these failures. One cause may relate to stroke injury-induced changes in the actions of drugs in the body following cerebral ischemia (Alavijeh et a., 2005; Conrado et al., 2010). Indeed, one report noted that approximately 40% of the failed clinical trials of

new drugs from a group of United Kingdom pharmaceutical companies occurred as a result of pharmacokinetic-related issues (Prentis et al., 1988). Further, the lack of efficacy of many neuroprotective drugs developed for stroke that failed clinical trials were shown to have very low therapeutic ratios when tested in rodents, calculated as the ratio between the minimum effective dose for rotarod impairment and that for significant neuroprotection from ischemic infarct (Dawson et al., 2001). Following a stroke, alterations of the metabolic pathway of exogenously administered drugs occur at nearly every level, ranging from limitations in ingestion to altered rates of absorption to disrupted enzymatic metabolism (Conrado et al., 2010). This suggests that the timetable of pharmacological actions of drugs, especially orally administered interventions, may be significantly impacted and possibly delayed. Also, genetic variants can modulate drug metabolism, therapeutic effectiveness, and treatment-associated risk for adverse events for agents commonly prescribed to stroke patients (Meschia, 2009). Indeed, several genetic factors are known to modulate the response to antiplatelet agents, statins, anticoagulants, and antihypertensive agents, sometimes reducing beneficial effects these interventions may have on stroke prevention of recovery. Thus, non-typical doses of a given drug may be required to exert the desired effect in the context of ischemic brain injury.

From a research perspective, these issues are problematic, given that the majority of preclinical investigations where drug discovery research takes place are conducted using in-bred rodent strains, tightly controlled methods for inducing cerebral ischemia, and routes of administration where many of these drug metabolism issues are obviated (Greenhalgh et al., 2011). While these approaches are key to isolating observed beneficial outcomes of an experiment to the intervention of interest, they also limit the translatability of such discoveries. Further, heterogeneous responses to clinical interventions can reduce the ability to detect meaningful pharmacologic action of a novel intervention for the broad stroke-patient population. This can be especially problematic when a drug has a narrow therapeutic margin, and can lead to the presumed failure of the new drug when in reality it may be very effective, but suited for a particular type of stroke and/or subpopulation of stroke patient. Validation of new stroke drugs in out-bred strains, as well as continued advances in genetic screening and individualized medicine, will likely improve translation of novel pharmacologic interventions. However, these efforts will be associated with significant expense. Indeed, as the field of molecular genetics is still nascent, genetic screening for drug responsiveness is not currently standard practice, resulting in high costs. Moving forward, these costs must be weighed with the known expenses associated with failed clinical trials.

Timing of drug administration post-injury is emerging as a potentially critical component of effective stroke therapy. Cerebral ischemic events induce changes in the permeability of the BBB that may affect drug concentrations at the target tissue (Greenhalgh et al., 2011). Importantly, this opening of the BBB can occur at multiple time points following injury and reperfusion, underscoring the importance of accurately pinpointing the time of injury and indicating the potential need to factor time-since-injury in the dosing of any pharmacological intervention administered. The trajectory of BBB permeability post-stroke can also be affected by other factors, such as the presence of an active infection associated with the ischemic event (McColl et al., 2008). Such observations suggest that post-injury time-points for maximal efficacy of a compound should be a consideration for any newly developed

neuroprotective agent. For example, pharmacologic recanulization agents should continue to be administered as soon as possible, whereas agents to promote the normalization of the monoaminergic system could be administered at a later time point and still impart their neurorestorative effects. Similarly, dose-titration of interventions across the recovery period may be necessary as stroke-induced disruptions to the gastro-intestinal system are attenuated with increasing time since injury (Conrado et al., 2010). Together, these findings highlight a need to reconsider the “one-size fits all” approach and move towards a more individualized medicine approach for the treatment of ischemic and hemorrhagic stroke, where factors such as genetic variants in drug responsiveness, etiology of and time since stroke, and the presence of mitigating/co-morbid factors are core features of the treatment decision process.

Limitations in the Field

The expansive range of stroke patients afflicted with executive dysfunction can likely be attributed to, in part, the heterogeneous nature of executive function, the diagnosis of its dysfunction, and its assessment post-injury. Also, variation among animal stroke models may influence the types of executive function domains affected. Perhaps the most prominent issue arises when trying to define executive function; although technical definitions have been established, there is still significant overlap among the behavioral phenotypes, neuroanatomical pathways, and neurotransmitter systems underlying the various components of executive function, especially when considering how many of these processes are inherently interdependent upon one another. This overlap makes it difficult to therapeutically target the cellular and molecular substrates that control specific components of executive function accurately. Compounding this is considerable heterogeneity in the diagnosis and assessment of executive dysfunction, as clinicians and pre-clinical researchers implement a variety of neurological scales and cognitive assessments used to test behavioral phenotypes of specific components and/or multiple components simultaneously, thus increasing the difficulty in deducing the differences between individual components. These limitations, combined with variation in animal model-induced physiologic and behavioral outcomes generates less than optimal translational validity. As such, increased optimization and standardization of animal stroke models and executive function diagnostic and assessment tools could improve upon these issues.

Conclusions and Future Directions

In summary, the devastating impacts of stroke and its secondary consequences are well-known, and with increasing prevalence require much attention from clinicians and basic scientists. Of the secondary consequences, impairment of executive function is a heterogeneous syndrome in which the simultaneous interplay of multiple cognitive processes that comprise one’s ability to reason and solve problems is often severely compromised. This impairment can prove detrimental to quality of life in stroke patients, as the components of executive function are necessary tenets of real-world functioning. Associated with these behavioral detriments, is known monoaminergic dysregulation following stroke, particularly within the DA-, NE-, and 5-HT-ergic systems. Variation within monoamine disruption is inherent, as impairment can happen at various stages during the neurotransmitter life cycle. However, to date, limited literature exists examining interactions

between stroke, monoamine disruption, and executive dysfunction. This knowledge gap is likely complicated by various parameters, such as age, sex, severity of infarct, location and size of the lesion, post-stroke time-point during which monoamine systems and executive functions are assessed following stroke (i.e., acute versus chronic assessments), and stroke-induced changes in the pharmacology of therapeutic interventions. Thus, given the known relationships between stroke, monoamine systems, and executive function, one may postulate that the factors comprise a linear relationship, wherein monoamine system modulation following stroke leads to executive function deficits. Moving forward, therapeutic intervention which targets not only one, but perhaps a combination of different monoamine systems at various levels of neurotransmitter regulation, may prove successful in ameliorating these stroke-induced deficits. Furthermore, careful consideration should be given when selecting which stroke model to implement, as different models emphasize distinctive structural and functional, brain-related characteristics within the human stroke population and therefore may impact both different components of executive function and monoaminergic neurotransmission in an unequal manner. Stroke model variation should also be well-advised during therapeutic development, as incommensurately impaired components may require different dosing regimens or perhaps differing therapeutic applicability altogether. As such, additional research to dissociate the different components of executive function impacted by stroke and standardization of assessments to evaluate these individual components, in conjunction with refinement and optimization of current animal stroke models, may enhance clinical translation of experimental research, and is warranted.

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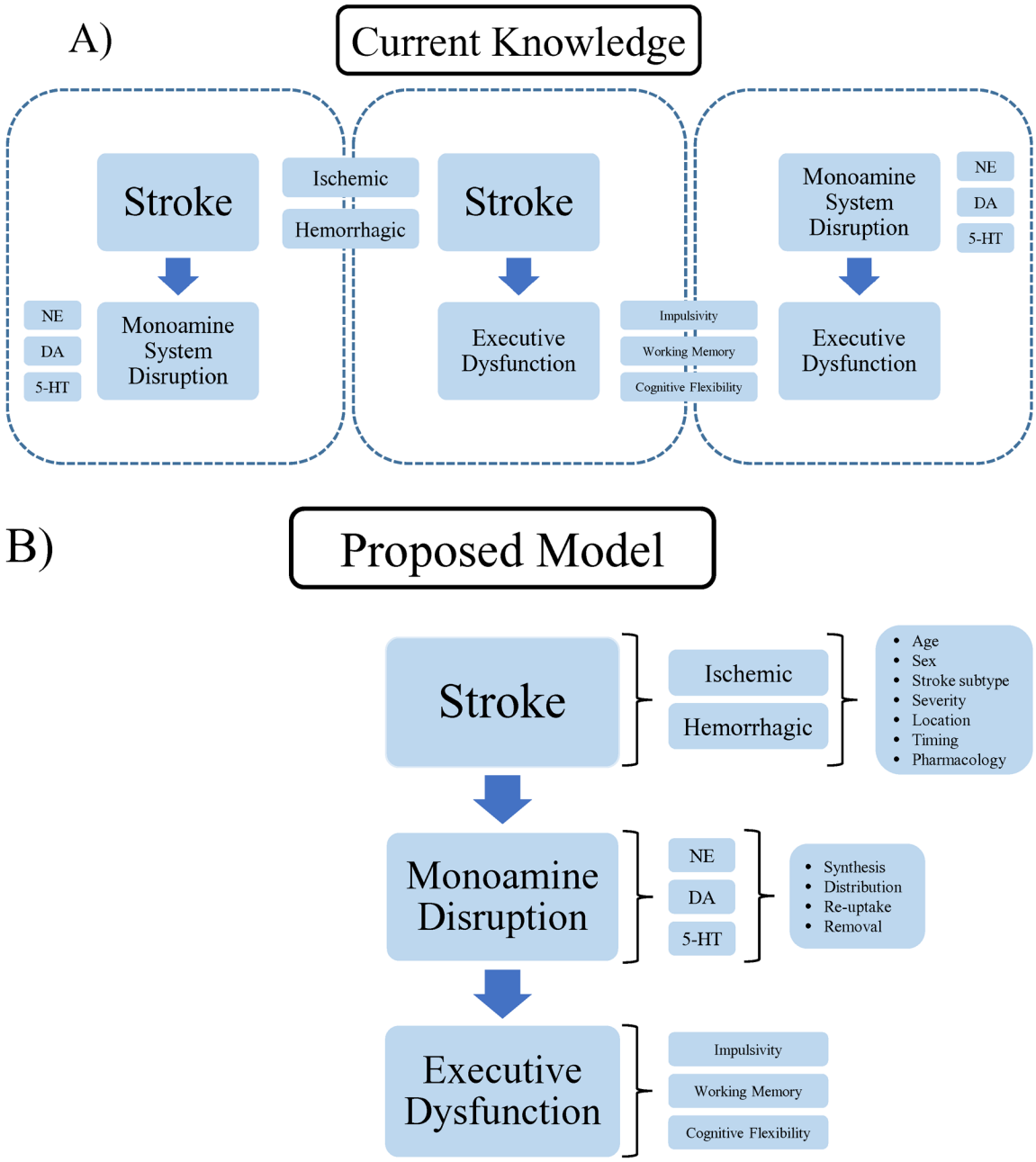

Figure 1.

A) Current knowledge of monoamine dysregulation and executive function impairment following stroke. A review of the literature reveals studies that address the following relationships: 1) monoamine neurotransmission (in particular, NE, DA, and 5-HT) disruption following stroke, 2) executive dysfunction associated with various models of stroke, and 3) monoamine neurotransmission modulation during executive function/dysfunction. Yet, currently, scant literature exists examining interactions between all three factors concurrently and the literature that does exist can be conflicting. This knowledge gap is likely complicated by various parameters that modulate stroke outcome, monoaminergic neurotransmission disruption, and executive function impairment, as well as, the potential

for disruption of multiple stages of monoaminergic neurotransmission (synthesis, distribution, re-uptake, and degradation). B) Proposed model of stroke-induced executive dysfunction. Given the known relationships between monoamine neurotransmission and executive function disruption post-stroke, in addition to well-established literature demonstrating changes in executive function following manipulation of one or more monoaminergic neurotransmitter systems, it is possible that a linear relationship in which stroke leads to executive dysfunction via changes in monoamine systems exists. Thus one or a combination of monoaminergic neurotransmitters and/or multiple levels of monoamine regulation may prove as viable therapeutic targets to ameliorate the spectrum of stroke-induced executive function deficits that may be realized. **NE:** norepinephrine; **DA:** dopamine; **5-HT:** serotonin.