Anosognosia in Hemiplegia: Toward a Process of Surrogate Decision-Making

by

Gabriella Paige Nutter

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This thesis was presented

by

Gabriella Paige Nutter

It was defended on

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and approved by

Mark R. Wicclair, PhD, Professor of Philosophy, Emeritus at West Virginia University and Adjunct Professor of Medicine at the University of Pittsburgh

Jason B. Rosenstock, MD, Professor of Psychiatry and Associate Dean for Medical Education, School of Medicine, University of Pittsburgh

Thesis Advisor: Lisa S. Parker, PhD, Dickie, McCamey & Chilcote Professor of Bioethics, University of Pittsburgh

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Anosognosia is a condition in which patients lack awareness of their illness or impairment. Anosognosia in hemiplegia (AHP)—an unawareness of one's one-sided paralysis—can occur following stroke. Without the ability to appreciate their paralysis and its consequences, patients with AHP lack the capacity to make certain decisions surrounding their stroke. However, AHP compromises patients' ability to appreciate their paralysis without necessarily restricting other cognitive capacities. As a result, AHP raises questions regarding whether and how patients may be allowed to authorize or refuse treatment or enroll in research. For incapacitated patients without an advance directive, decision making authority is transferred to patients' surrogates who would make decisions according to the substituted judgement standard. The outcome of employing this standard is only as reliable as the evidence on which is it based. Though patients with AHP fail to appreciate the experience and implications of paralysis, patients may retain specialized knowledge of their values and preferences that they can share with their surrogates even in their anosognosic state. This paper will demonstrate that patients with AHP can be involved in the decision-making process and that doing so assists surrogates in reconstructing these patients' values and preferences. The first section will introduce anosognosia and some barriers to its classification before focusing on AHP. In the second section, I will argue that patients with AHP who lack decisional capacity can nevertheless be engaged in questioning involving hypothetical situations to solicit their view of their interests thereby contributing to decisions to manage their stroke in the acute setting. While surrogate decision-making is an appropriate strategy in the clinical setting,

it is less justifiable in research owing to the added risks and burdens of participation for the benefit of others. The third section will demonstrate how engaging prospective subjects with AHP in the decision-making process may expand the range of research in which it is ethically justifiable for surrogate decision-makers to enroll people with AHP, if such enrollment is in line with the subjects' values and preferences, or health-related interests.

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1.0 Introduction

Anosognosia is a disorder in which one is unaware of one's illness or impairment. Patients with anosognosia often fail to seek or accept medical attention. Because anosognosia compromises patients' ability to appreciate their illness or impairment without necessarily restricting other cognitive capacities, anosognosia raises questions regarding whether and how patients may be allowed to authorize or refuse treatment or enroll in research. This project will consider these questions and their ethical implications.

Anosognosia is a highly heterogenous, multifactorial disorder. It is suspected that there are various illnesses or injuries about which one can be anosognosic, which contributes to the variable expression of the phenomenon. Determining whether these are different types of the same phenomenon, namely anosognosia, or different phenomena entirely is complicated by several factors. The first section of this project will discuss these factors before focusing only on anosognosia in hemiplegia—a lack of awareness of one's one-sided paralysis following stroke. It will conclude by discussing how anosognosia in hemiplegia affects functional outcomes for patients.

A lack of awareness of paralysis following stroke jeopardizes patients' ability to appreciate their stroke and its consequences. As a result, awareness of one's paralysis following stroke is relevant for decisions regarding the treatment of one's hemiplegia, and sometimes stroke, without which one's capacity to make decisions regarding the treatment of one's hemiplegia and stroke is impaired. However, anosognosia in hemiplegia does not entail an overall impairment in patients' awareness, nor does the phenomenon completely compromise patients' other capacities. Therefore, the second section will analyze how anosognosia in hemiplegia compromises the ability

of patients to provide informed consent to acute treatments for stroke or hemiplegia, but how patients with anosognosia in hemiplegia may nevertheless engage with the decision-making process. This may be as simple as asking the patient to consider hypothetical scenarios and the respective level of care they would prefer. This section will argue that by including patients in the decision-making process to the extent that they are able, surrogates are assisted in their reconstruction of patients' values and preferences relevant to the decision at hand. Therefore, a decision will more reliably reflect the decision patients would make if they were aware of their condition.

While surrogate decision-making is an appropriate strategy for making decisions in the clinical setting, surrogate decision-making in the research setting may, at least in some cases, be ethically problematic. This is because research is not designed primarily for the benefit of research subjects, but instead for third parties. There is reason for concern when considering permitting someone (a surrogate) to volunteer another (a patient) to benefit a third party (e.g., future generations of patients with the condition under study). On the other hand, some clinical research does have the potential to provide direct (i.e., therapeutic) benefit to those enrolled in the study. This third section will focus on surrogate decision-making for informed consent to research participation. After discussing the issues in general, it will consider whether anosognosia in hemiplegia poses a particular problem for enrolling prospective subjects in research. The current consensus view prohibits surrogates from enrolling incapacitated subjects in research with a greater than minimal risk of harm unless the research has the potential to provide subjects with a direct benefit. This section will argue that surrogates should be able to enroll prospective subjects with AHP in research studies with greater than minimal risk of harm if such participation will reliably fulfill prospective subjects' values and preferences even in the absence of the prospect of

direct benefit. Surrogates can gain reliable knowledge of prospective subjects with AHP' values and preferences by asking the patient to consider hypothetical research scenarios. This knowledge allows surrogates to make decisions in accordance with what are subjects' actual values and preferences and not their temporary values and preferences misguided by false, anosognosia-based beliefs. A decision to enroll in research, if supported by the hypothetical scenario, protects subjects with AHP from undue harm and ensures that the interests of these incapacitated subjects are respected.

2.0 An Introduction to Anosognosia

Stroke is the second leading cause of deaths worldwide and the fifth leading cause of deaths in the U.S. (Sattin et al., 2022). It occurs as the result of impaired passage of blood through vessels in the brain. Ischemic stroke is caused by deficient supply of blood and oxygen to the brain, wherein reduced blood flow inflicts cellular stress, quickly leading to cellular death and loss of neuronal function. Hemorrhagic stroke, on the other hand, is caused by bleeding from blood vessels in the brain, whereby blood accumulates and produces a toxic effect on the vascular system (Lo, Dalkara & Moskowitz, 2003; Kuriakose & Xiao, 2020). Hemiplegia, characterized as an inability to move one side of the body, is a common sequela of stroke. Hemiplegia accompanies first stroke in 70-85% of patients (Dobkin, 2003). The location of the stroke in the brain will determine the location of paralysis in the body. For example, paralysis will occur on the side of the body opposite to the side of the brain damaged by stroke (American Stroke Association, 2019).

Unawareness of one's hemiplegia is often reported following brain lesions[1] or stroke (Cocchini, Beschin & Della Sala, 2002). Consider the following excerpt from a case report of Mrs. P, a hospitalized middle-aged woman who had suffered a right hemisphere stroke, resulting in complete paralysis on the left side of her body. Specifically, she was bedridden and unable to move. In addition to these impairments, Mrs. P cannot acknowledge her paralysis. A physician

[1] Brain lesions are areas of damaged brain tissue that result from brain injuries or medical conditions and disrupt normal brain functions in the area of the lesion (Berti, Garbarini, & Neppi-Modona, 2023).

(MS) met with Mrs. P three days after her stroke and recorded the content of that interview as follows.[2]

> **MS:** Can you tell me why you're in hospital?
> **Mrs. P:** Apparently I had a stroke; that's why I'm here.
> **MS:** That's right. But why did you say 'apparently'. Do you agree that you've had a stroke?
> **Mrs. P:** Yes, but I don't feel any symptoms. What do you feel? How are you supposed to feel?
> **MS:** Well, one of the most common consequences of a stroke is paralysis; you get loss of movement in an arm or a leg. Are you having those symptoms?
> **Mrs. P:** [Lifts up her paralyzed left arm with her intact right arm.] Here, they [the other doctors] can see; I'm lifting my arm up.
> **MS:** You're lifting it up so that the doctors can see?
> **Mrs. P:** Yes.
> **MS:** So are you showing them that you can move that arm or that you can't move that arm?
> **Mrs. P:** I can move it.
> **MS:** But you're lifting it by lifting it with this [right] hand. Can you lift it by itself?
> **Mrs. P:** I lift it with my mind.
> **MS:** With your mind?
> **Mrs. P:** [Nods.]
> **MS:** And when you lift it with your mind, do you actually see it and feel it moving?
> **Mrs. P:** Yes.
> **MS:** So if I had to ask you the question 'Is this arm working normally or not?' – what would your answer be?
> **Mrs. P:** No.
> **MS:** No, it's not working normally?
> **Mrs. P:** [Shakes her head.]
> **MS:** Okay; what's the matter with that arm?
> **Mrs. P:** Nothing. There's nothing wrong with it.
> **MS:** There's nothing wrong with it?
> **Mrs. P:** Because I can move it.

This phenomenon of unawareness of one's neurological dysfunction was first described regarding blindness (von Monakow, 1885; Anton, 1899) and deafness (Anton, 1899). An early account of that phenomenon in cortical blindness details how "initially [the patient] thought that

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[2] This clinical vignette is excerpted from a real clinical case reported on by Turnbull, Fotopoulou, & Solms (2014). I use it here to illustrate the phenomenon of anosognosia with a concrete example of its clinical manifestation and to highlight the mental confusion Mrs. P experiences as attention is drawn to her deficit.

he was in a dark pit or cellar and shouted for light and fire. Later, he appeared to have become accustomed to the visual hallucinations and so the notion that he could not actually see anything did not reach his awareness. He complained that he was old, stupid and weak – but he never articulated that he was blind" (Marková & Berrios, 2014 for translation). Constantine von Monakow (1885), who documented that account, attributed the patient's unawareness to brain lesions, however the unawareness was not conceptualized as an independent phenomenon. Instead, it was viewed as a symptom of cortical blindness for which brain localization was sought.

In contrast to this earlier description, Anton (1899) differentiated the unawareness of dysfunction as an independent symptom and classified it as a phenomenon in its own right.[3] By 1914, neurologist, Joseph Babinski, granted this phenomenon the name "anosognosia." Babinski described the cases of two patients, each with paralysis on one side of their body, and each with an unawareness of this deficit. Much like Mrs. P above, these patients demonstrated an ability to move their functioning arm, the right, but either ignored or offered peculiar explanations to instructions to move their arm on the side affected by the paralysis, the left. For instance, when attention was drawn to the affected arm, one of Babinksi's patients responded, "It's that [the paralyzed arm] goes less quickly than the other one" (1918). The lack of awareness following hemiplegia became well-known as "anosognosia," which is more than a simple unawareness of paralysis. Babinski argued that anosognosia describes a resistance to recognition, which persisted despite relatively preserved intellect in his patients (Babinski, 1914, 1918).

[3] For his contributions, Anton's syndrome or Anton-Babinksi syndrome was named after Gabriel Anton and is reserved for patients who lack awareness about their vision loss, secondary to occipital lobe insult. It is a type of anosognosia, namely visual anosognosia.

Anosognosia occurs in 10% to 18% of hemiplegic patients, with a higher frequency occurring in right brain damaged patients (Baier & Karnath, 2005). Anosognosia in hemiplegia is highly specific in that hemiplegic patients are typically only unaware of their hemiplegia related to their stroke or focal lesion, while remaining aware, and sometimes even hypochondrial, with regard to other impairments and chronic ailments (Bisiach et al., 1986; Turnbull, Fotopoulou & Solms, 2014).

Anosognosia in hemiplegia is known to take many forms other than a complete failure to recognize paralysis. One patient might verbally deny their impairment but engage in behaviors consistent with paralysis, while another might verbally accept their paralysis only to behave in a way which is inconsistent with their paralysis (Orfei et al., 2007). Frequently, however, both types of patients present with disturbed mood, affect, or motivation (Jenkinson, Preston & Ellis, 2011). Anosognosia in hemiplegia is often considered a temporary condition occurring in the acute and post-acute phases following stroke, which can fluctuate over time (Cocchini, Beschin & Della Sala, 2002; Jenkinson, Preston, & Ellis, 2011). It is rare for anosognosia in hemiplegia to persist chronically, but studies have recorded anosognosia in hemiplegic patients after about sixty days (Bakchine, Crassard, & Seilhan, 1997, Berti et al., 1998), eighty-four days (Levine, Calvanio, & Rinn, 1991), "1 year" (Cocchini, Beschin & Della Sala, 2002), and even "several years" (Babinski, 1914) following the initial stroke or trauma.

While most commonly used to describe the right hemispheric stroke patients, anosognosia appears to occur in many other serious neurological conditions including aphasia (Dean et al., 2017), traumatic brain injury (Prigatano and Altman, 1990; Sherer et al., 1998), mild cognitive impairment (Ries et al., 2007), Alzheimer's disease (Vogel et al., 2004; Starkstein, 2014; Hanseeuw et al., 2020), and Parkinson's disease (Maier & Prigatano, 2017). Although one can be

unaware about a wide range of conditions, anosognosia is considered to be especially common in dementia as a more or less inevitable feature of the condition (Wilson et al., 2016). In spite of profound cognitive dysfunction and impaired activities of daily living, patients with dementia might not recognize their impairments (Rankin et al., 2005). An unawareness of memory deficits is often reported in this patient group; however, in contrast to anosognosia following stroke, a defining feature of anosognosia in dementia is that it lacks specificity—that is, the unawareness of impairment may vary across multiple functional domains causing these patients to underestimate their deficits in multiple areas (Wilson et al., 2016). Patients with dementia will often unknowingly engage in confabulations—memories displaced in time or claims lacking a basis in reality (El Haj & Larøi, 2017). While different definitions have been proposed (Gilboa, 2010), confabulations tend to refer to the production of statements or actions that unintentionally do not reflect patients' history, background, and present situation (El Haj & Larøi, 2017). Because these patients are not aware of their confabulations, they tend to act on them. As awareness of their cognitive and functional abilities becomes impaired, these patients may engage in activities beyond their capacity, thereby exposing them to dangerous situations. Starkstein and colleagues (2007) found a threefold increase in the risk of dangerous behaviors in patients with dementia in Alzheimer's disease, defined as any behavior that brought about physical harm. As a result, patients rely heavily on caretakers to monitor their safety behaviors. Anosognosia in dementia, and in other disorders involving neurocognitive decline, is associated with increased hours of informal care, greater use of support services, and increased total family care costs (Hanseeuw et al., 2020). This burden is exacerbated over time because patients' unawareness tends to become more pronounced with the progression of dementia. However, there is no linear relationship between the severity of patients' unawareness and the progression of dementia (Amanzio et al., 2013).

Additionally, anosognosia is often reported as occurring in psychiatric conditions, like schizophrenia (Amador, 2000) and bipolar disorder (Fennig et al., 1996; Ibrahim et al., 2020). It is fairly common with schizophrenia, occurring in about 57% (Amador et al., 1994) to 98% (Jablensky et al., 1992) of patients. Despite experiencing hallucinations, delusions, and other pathological behaviors, these patients may adamantly refuse to admit that they experience a mental illness (Nasrallah, 2020). Anosognosia about one's mental illness is modality specific: patients might be aware of some aspects of their condition, like that they suffer from delusions, while lacking awareness of others, like hallucinations and mood disturbances (Amador & Paul-Odouard, 2000).

Awareness in patients with psychiatric conditions can fluctuate. For example, patients with bipolar disorder can exhibit a phase-dependent type of anosognosia wherein they are unaware of their deficits during the manic phase of their disorder, only to switch to an awareness of their condition during the depressive phase (Fennig et al., 1996; Ibrahim et al., 2020; Nasrallah, 2022). In contrast to patients with dementia, some patients who lack awareness about their mental illness are able to regain awareness of their disorder and its consequences. Ibrahim and colleagues (2020) found that awareness improved with treatment in bipolar patients. Similarly, treating and preventing psychotic episodes in patients with schizophrenia is associated with improved awareness of their disorder (Emsley et al., 2008). Without this improvement, a lack of awareness is associated with decreased adherence to treatment, an increased number of hospitalizations, relapses, and psychotic symptoms, and involuntary commitment (Amador, 2000; Rickelman, 2004). As a result, these patients are stuck in a loop whereby treatment would improve their awareness of their disorder, but in order to begin or adhere to treatment they require an awareness of their disorder.

2.1 The Many Faces of Anosognosia

The diversity of behaviors associated with anosognosia—and the range of abilities and conditions about which patients with anosognosia are unaware—raises the question of what really counts as anosognosia. Even in discussing these few examples of what appear to be anosognosia, it becomes clear that anosognosia is a highly heterogenous and multifactorial disorder for which different manifestations in varying degrees prevent the development of a single diagnostic entity (Orfei, et al., 2007; Little, 2020). It is unclear whether we are talking about one phenomenon with different causes, or multiple different phenomena (Marcel, Tegnér & Smith, 2004). There are several reasons for this lack of clarity that results in the lack of a unitary conception of anosognosia: the complexity of the concept of awareness (extension and partiality), current methods for assessing anosognosia (specificity), and the variety of terms used to describe anosognosia.

2.1.1 The Complexity of Awareness

First, even with regard to one manifestation of anosognosia, the literature describes a diversity of behaviors associated with the phenomenon. A coherent understanding of these behaviors is difficult given the complexity of the concept of awareness. This results in a lack of consensus regarding the characterization of anosognosia.

Schacter & Prigatano (1991) discuss five issues regarding the different forms of awareness: levels of awareness, partial/implicit knowledge of deficits, specificity of unawareness, neural bases of unawareness and defensive denial. The first two issues are relevant to this discussion on the complexity of awareness. First, the level of awareness, or what others have called the extension of

anosognosia (Marcel, Tegnér & Nimmo-Smith, 2004), is the idea that unawareness of one's condition can be with regard to at least two things—one can be unaware of the condition itself or unaware of some of the consequences of one's condition. For example, Rubens & Garret (1991) discuss the case of aphasic patients who are aware of their language deficit when prompted, but struggle to notice when they have made a linguistic error. The awareness that one has an impairment is distinct from the awareness of particular failures in ability. Clinicians and investigators do not always parse out these, at least, two domains.

However, it might be incorrect to describe patients as being "aware" or "unaware" of their deficit or a consequence thereof. Awareness might not be an all-or-nothing concept, and describing it as such does not do justice to the subtleties of awareness and awareness impairments. This is what Schacter & Prigatano (1991) call partiality—the idea that awareness exists on a sliding scale so that one can demonstrate only partial awareness toward one's deficit. Partial awareness can be described according to two distinct senses: a type of awareness that is less than fully conscious, or a lack of awareness of a component of a deficit with complete awareness of other components. Partial awareness in the second sense is typically described in relation to stroke patients with anosognosia. For example, patients with anosognosia in hemiplegia are only unaware of one component of their stroke—their hemiplegia. Partial awareness in the first sense, however, is addressed less often concerning anosognosia, but is nevertheless an important feature. This first sense is demonstrated by the ability of patients with anosognosia to retain some level of implicit awareness of their deficit. These patients might not explicitly acknowledge their deficit but still behave in a way which is consistent with them possessing some awareness of their deficit. For example, a patient with hemiplegia might attempt to execute a bimanual task with a unimanual strategy despite a repeated inability to acknowledge their paralysis (Cocchini et al., 2010).

2.1.2 The Assessment of Anosognosia

The complexity of awareness makes it difficult to assess. This issue is addressed by Schacter & Prigatano's specificity of unawareness, which describes how the many aspects associated with anosognosia necessitate use of a wide range of investigative methods, each of which may reinforce different ways of understanding anosognosia. If awareness can be dissociable into components, then it may be that different tools for assessment of anosognosia tap into different aspects of unawareness, producing highly variable results regarding what behaviors are associated with anosognosia and how anosognosia is produced by the brain. Although many questionnaires and diagnostic methods have been developed over time to assess anosognosia, they often employ heterogenous selection criteria and assessment modalities. As a result, the characterization of anosognosia is inconsistent across different assessment tools (Schacter & Prigatano, 1991). For example, a wide variation in the incidence of anosognosia in hemiplegia—ranging from 17% to 58% across seven studies—is reported in the literature, owing to the type of assessment tool used and the fact that different investigators score patients differently even when using the same assessment tool (Baier & Karnath, 2005). Some studies categorize "mild anosognosia," (unawareness reported only after specific questioning) as indicative of anosognosia, while other studies exclude "mild anosognosia" because other assessment tools are able to demonstrate how patients with mild anosognosia are, in fact, aware of their hemiplegia when asked about the strength of their limbs. The lack of conceptual clarity regarding the phenomenon of anosognosia is reinforced by the variable use of diagnostic methods.

2.1.3 Defining Anosognosia

Lastly, depending on the condition about which one is anosognosic, different terms are used to describe the phenomenon. As previously discussed, the term ‘anosognosia’ was first used to describe a lack of knowledge, awareness, or recognition of motor impairment in patients following stroke (Babinski, 1914). This usage denotes a neurological condition in which brain localization is apparent. However, a similar expression of unawareness of illness is exhibited in other conditions not of the strict neurological kind. Use of the term is subject to the theoretical positions of those employing it, the investigators of the different conditions, each of whom provides alternate or even supplementary language to identify and understand unawareness of illness (Amador et al., 1991). As a result, multiple terms have been used more-or-less interchangeably in an attempt to capture unawareness of one’s condition, i.e., anosognosia. ‘Neglect’, ‘lack of insight’, and ‘denial’ are all used, yet these different terms might represent distinct aspects of anosognosia if not entirely separate phenomena (Vuillemier, 2004). The variety of terms associated with anosognosia exacerbates the inability to reach consensus about what is included under the heading of anosognosia and what is not.

2.1.3.1 Neglect

Since its initial detection, anosognosia was thought to involve some perceptual defects like hemianaesthesia (inability to perceive touch sensations from one side of the body), hemianopia (blindness over half the visual field), or hemineglect. In clinical practice, hemineglect is recognized as the inability to directly attend to a side of one’s body that is opposite to the site of a brain lesion; it is broadly referred to as ‘neglect’. Patients with neglect cannot react, respond, or look for stimuli presented to one side of their body (Jenkinson, Preston & Ellis, 2011). ‘Neglect’

is most often used in the context of anosognosia in hemiplegia. The idea here is that patients with anosognosia cannot acknowledge their impairment because they lack the perceptual ability to become aware of, in the case of hemiplegia, a paralyzed limb on one side of their body (Turnbull, Fotopoulou & Solms, 2014).

While this account of anosognosia was previously used to explain its origin, research since has demonstrated its lack of empirical support. Neglect is correlated with anosognosia in hemiplegia and the two frequently occur together. However, neglect without anosognosia, as well as anosognosia without neglect, is common. Therefore, the two phenomena are distinct, even though they often present together due to the nature of the underlying injury or trauma. Neglect may facilitate anosognosia, but it is neither a necessary nor sufficient condition (Levine, Calvanio & Rinn, 1991; Bisiach, et al., 1986).

2.1.3.2 Insight

A "lack of insight" or "poor insight" are other phrases used to describe anosognosia. They are most often used when describing anosognosia for psychiatric conditions, like schizophrenia or bipolar disorder. 'Insight' describes patients' comprehension of the nature and causes of their problems. Poor insight is a cardinal symptom of psychotic disorders, while good insight is associated strongly with better quality of life for patients with mental illness. As a result, the promotion of insight is viewed as an important goal in treatment (McGorry & McConville, 1999). Insight, however, is particularly difficult to define despite the frequency with which it is used in describing mental illnesses (Fennig et al., 1996). David (1990) describes insight employing three overlapping dimensions: the recognition that one has a mental illness, the ability to relabel unusual mental events as pathological, and adherence to treatment. Others analyze insight according to its descriptive and experiential dimensions (Mohamed, Bertman & Hubbeling, 2022). Amador &

Gorman (1998) use the term interchangeably with ‘awareness’, describing a lack of insight as a lack of awareness of having an illness, specific signs, or symptoms; an ignorance of the consequences of the disorder; or a lack of agreement with health professionals that treatment is necessary.

Clearly, there are major similarities between “lack of insight” in psychiatric conditions and “anosognosia” in a broad sense, suggesting that “lack of insight” or “poor insight” might be a type of anosognosia (Rickelman, 2009; Mohamed, Bertram & Hubbelling, 2022). Indeed, there is some evidence to suggest that the neurobiological and cognitive correlates of anosognosia overlap somewhat with the pathophysiology of schizophrenia (Lehrer & Lorenz, 2014; Nasrallah, 2022). Such evidence would justify the extension of anosognosia to schizophrenia-related insight deficits, however, further investigation is needed before making this extension. Therefore, given the variable use of both terms and the lack of consensus regarding what characteristics should count as anosognosia, it is not clear that a finding of a lack of insight in a psychiatric context is always the equivalent of diagnosing anosognosia.

2.1.3.3 Denial

It is frequently argued that unawareness of one’s deficit reflects a motivated defense mechanism, and as a result, that anosognosia in a broad sense is better understood as a type of denial (Weinstein, 1991). Denial in this context is “the defensive distortion of one’s perception of some aspect of one’s environment, of what is usually called external reality” (Freud, A., 1936). Anosognosic patients are confronted with a profoundly challenging deficit. Instead of adjusting to their new condition, an anosognosic patient “takes the path of least resistance” and represses any input demonstrative of their deficit (Turnbull, Fotopoulou & Solms, 2014). In other words, denial is not so much about a lack of awareness, but rather a mechanism to avoid psychic distress and a

method of coping with one's acquired impairment (Kortte & Wegner, 2004). This is referred to as the psychological defense hypothesis regarding anosognosia. Denial of an illness can certainly be adaptive or functional in this way. For example, in one study, lung cancer patients with moderate or increasing levels of denial over time reported better social outcomes, less anxiety, and less depression than lung cancer patients with a low level of denial (Vos et al., 2009). In women with nonmetastatic breast cancer, denial was similarly found to alleviate psychological distress, even demonstrating an association with longer survival (Kreitler, 1999). Therefore, many patients use denial to undermine or avoid medical conditions, but is this the same thing as anosognosia?

Arguably, a mechanism of denial underlying anosognosia certainly explains many of anosognosia's peculiar features. For example, it might explain how some patients retain implicit awareness of their deficit while explicitly denying their impairment. In a set of pertinent experiments, Ramachandran (1996) sought ways to reinstate awareness in patients with anosognosia in hemiplegia. In one experiment, he stimulated the vestibular nerve of a patient with anosognosia in hemiplegia by sending cold water down the ear canal opposite to the side of the brain damaged by stroke. After a few minutes the patient was able to admit to their paralysis. More importantly, the patient admitted to being paralyzed for the past several days. Therefore, even though the patient denied their paralysis prior to the procedure, information about their motor impairment was nevertheless being encoded somewhere (Ramachandran & Blakesee, 1998). This is their implicit knowledge. Unfortunately, once the effects of the procedure wore off, the patient returned to their anosognosic state. While the patient retained memory of the procedure, the patient could not remember that they had just admitted to being paralyzed. The defense hypothesis would argue that because the patient selectively recalls the procedure, except the information that

confirms their paralysis, the patient is purged of the emotional consequences of awareness of their deficit.

In another experiment, Ramachandran (1996) delivered an injection into the arm of a similarly afflicted patient. The patient was informed that the contents of the injection produce paralysis as a side effect lasting a few minutes when, in fact, the injection was filled with a saline solution. Following the injection, the patient reported—for the first time since the onset of anosognosia—that their arm was not moving. The only thing that changed for the patient was a change in their explanation for their paralysis—that an injection produced a temporary side effect of paralysis. Arguably, knowing that such a profound impairment is only temporary relieves its emotional burden, thereby allowing knowledge of the impairment to enter into explicit awareness.

However, substantial evidence argues against this interpretation of anosognosia. One of the first attempts to distinguish anosognosia from denial of illness relied on patients' patterns of reactions when presented with information about their injury. Prigatano & Klonoff (1998), through their clinical observations, found that patients with denial of their disability exhibit partial or implicit knowledge of their impairments, resist or become angry when provided with feedback regarding their impairments, and struggle to work with new information about themselves. In contrast, patients with anosognosia lack information about themselves, are confused when given feedback regarding their impairments, and are either cautious or indifferent when asked to perform tasks with new information about themselves.

Beyond its clinical presentation, there is evidence to suggest that anosognosia is anatomically different from psychogenic denial. Brain imaging studies reveal neural substrates and networks functioning differently in patients with anosognosia as opposed to those without (Starksetin et al., 1992; Ries, 2007; Starkstein, 2014; Nasrallah, 2022). Lesion studies reveal

damage to the frontal, temporal, and parietal cortex, as well as to the insula, and other sub-cortical regions in patients with anosognosia in hemiplegia (Berti et al., 1998; Hartman-Maeir, Soroker, & Katz, 2001; Berti et al., 2005; Karnath, Baier, & Nagele, 2005; Fotopoulou et al., 2008). Damage to the prefrontal cortex, and front-striatal circuits reveal the possible interaction of systems involved in perspective-taking (Besharati et al., 2016), body representation (Karnath, 2005), reality checking, and belief updating (Vuillemier, 2004; Jenkinson et al., 2011) in addition to damage in brain centers responsible for motor control and movement awareness of intended motor acts. Additionally, widespread network dysfunction is exhibited by anosognosic patients and is thought to contribute toward sensory-motor deficits (Pacella et al., 2019; Monai et al., 2020).

Another account implicates the higher incidence of anosognosia in hemiplegia after right hemisphere damage as opposed to left hemisphere damage (Hartman-Maeir, Soroker, & Katz, 2001). Following the psychological defense hypothesis regarding anosognosia, we might expect hemiplegic patients with left hemispheric damage to demonstrate denial comparable to patients with right hemispheric damage because they both suffer from impairments of equal magnitude. However, this is not the case: anosognosia is more frequent and more severe after right hemispheric lesions (Orfei, Caltagirone, & Spalletta, 2009).

Another issue for the defense hypothesis regarding anosognosia is the selectivity of anosognosia: patients can be unaware of one deficit while aware, and even overly perceptive, of other equally serious deficits (McGylnn & Kaszniak, 1991). If anosognosia is manufactured out of a motivated protective mechanism, it does not make sense for that mechanism concurrently to allow the awareness of other serious deficits.

There is a third way of understanding anosognosia that takes into account these biological and clinical features while not completely rejecting the role of psychological mechanisms.

Turnbull and colleagues (2014) advocate for the view that anosognosia is the result of damage to cognitive regulatory mechanisms of emotion. They argue that without properly functioning cognitive regulation of emotion, emotion is allowed to influence cognition. Damage to the part of the brain that represents the world as it is allows patients to perceive things as they want them to be instead of as they really are. Turnbull and colleagues draw this conclusion partly from growing evidence of the role of right hemispheric systems in emotion regulation. If emotion regulation occurs predominantly in the right hemisphere, this account of anosognosia would explain why it is seen more frequently in patients with right hemispheric damage.

What is particularly interesting about this perspective—and relevant for this project—is that this account deviates from the idea that anosognosia is either denial or it is not. It makes room for psychogenic features of anosognosia, but argues that they arise not from a motivated psychological mechanism but from the inability of cognitive systems to function properly following damage or disturbance. While the literature on anosognosia has largely moved away from the idea that anosognosia is a type of psychogenic denial, it will be important to this project not to discount some of anosognosia's psychological features.

2.1.4 Conceptualizing Anosognosia for This Project

In summary, the phenomenon of being unaware of one's deficit seems to be present in a variety of disorders. Determining whether these are different types of the same phenomenon, namely anosognosia, or different phenomena entirely is complicated by several factors: the aspect about which one is unaware, how that unawareness is assessed, and the theoretical framework through which the unawareness is described and understood. Due to these complexities and a lack of consensus in the literature, I will understand anosognosia broadly as the unawareness of

dysfunction. I will restrict my use of terminology to 'anosognosia' and 'lack of awareness' or 'unawareness' and will focus the remainder of this discussion on anosognosia about one condition—hemiplegia. By focusing on only one condition, I will be better able to address how anosognosia affects informed consent and thus clinical care and research involving patients with anosognosia.

Hemiplegia is a condition well-suited to this project's focus on the ethical relevance of anosognosia for decision-making. In hemiplegia, anosognosia is usually resolvable over a few days to weeks, whereas anosognosia in psychiatric conditions (e.g., schizophrenia) fluctuates on a more unpredictable timeline, and anosognosia in disorders of neurocognitive decline progressively becomes more severe with little to no hope of remission. Anosognosia in hemiplegia is highly functionally specific—awareness is one of few cognitive faculties that become impaired. As a result, the discussion may focus on the effect of this lack of awareness on decisional capacity without having to account for the complications associated with other cognitive impairments. In contrast, with schizophrenia, for example, a lack of awareness of one's deficits is complicated by other neuropsychological symptoms, which impair cognitive and emotional regulation. Therefore, the ethical relevance of anosognosia in hemiplegia appears to be less obscured by other aspects of the disorder about which one is anosognosic. Nevertheless, the analysis of how we should think of anosognosia in hemiplegia should provide a foundation for consideration of assessment of decisional capacity and the process of informed consent for other manifestations of anosognosia.

2.2 Anosognosia in Hemiplegia

Anosognosia in hemiplegia (AHP) involves more than an unawareness of one's paralysis. Patients with AHP demonstrate a real resistance or reluctance to address the deficit (Vuilleumier, 2004). However, this resistance does not extend to their recognition of their symptoms in general. Typically, it is only their hemiplegia related to their stroke that evades patients' awareness, while they may be aware of their other stroke symptoms (Marcel et al., 2004). Additionally, these patients may be aware of, and frequently complain about, the presence of other ailments unrelated to stroke, like back pain or insomnia. They will continue to acknowledge their chronic conditions while remaining unaware of their paralysis (Bisiach et al., 1986; Ramachandran & Blakesee, 1998; Turnbull, Fotopoulou & Solms, 2014).

Patients with AHP may show different degrees of awareness of their motor impairment, ranging from an unrelenting unawareness of the deficit to emotional indifference, or anosodiaphoria, in which they can admit to their motor impairment without concern (Babinksi, 1914; Bisiach & Geminiani, 1991; Berti et al., 1998). As a result, patients with AHP can have a disturbed mood or affect, or exhibit reduced motivation leading to an increase in depression (Starkstein et al, 1992) or apathy (Levine, Calvanio, & Rinn, 1991). Even in the case of severe unawareness of deficit, some patients with AHP demonstrate implicit awareness of their deficits: while patients may explicitly deny their paralysis, they may unconsciously process some aspects of their deficit (Fotopoulou et al., 2010). For example, Cocchini and colleagues (2010) found that some hemiplegic patients would attempt a series of bimanual tasks as if they could use both hands, even though they demonstrated an awareness of their deficit on a self-report questionnaire. Other hemiplegic patients exhibited the opposite result—namely, they would attempt bimanual tasks only using one hand, their functioning hand, despite their lack of awareness of their deficit.

Similarly, Fotopoulou and colleagues (2010) examined fourteen stroke patients with left-sided paralysis and found that awareness dissociated into implicit and explicit awareness, and that hemiplegic patients with anosognosia could have one and not the other.

A similar effect is seen in the memories of patients with AHP. This was demonstrated earlier by Ramachandran's (1996) experiments, in which anosognosic patients gain temporary awareness of their impairment. Either by stimulating patients' vestibular nerve or by deceiving patients into thinking an injection would cause them temporary paralysis, Ramachandran was able to reinstate awareness in his patients, albeit temporarily. Similarly, psychotherapy may induce temporary awareness in patients with AHP (Kaplan-Solms & Solms, 2000). In their temporary state of awareness, patients not only acknowledge their hemiplegia, but they are able to acknowledge their hemiplegia since its onset. For example, Mrs. M, one of Ramachandran's patients in these experiments, told him, "[my arm] has been paralyzed continuously for several days now," during her moment of awareness following caloric stimulation (1996). Mrs. M was able to recall the memory of her experience—that she had been paralyzed for several days—even though this memory was not available to her until now. Mrs. M demonstrates how the experience of hemiplegia is nevertheless being encoded somewhere despite patients' fervent lack of awareness of their paralysis.

Unfortunately, these moments of awareness are temporary. Within minutes or a few hours patients return to their state of unawareness. Once patients return to their anosognosic state, they are able to recall the procedure except that they cannot recall their paralysis or that they had acknowledged their paralysis moments before. Mrs. M, for example, was asked about her procedure eight hours following its conclusion, to which she replied, "Yes. They put water in my ear; it was very cold," and "I said my arms were okay." The memory of her paralysis had returned

to its place of hiding and was replaced by a false memory—that instead of acknowledging her paralysis, she asserted against it. False memories occur when patients recall an event that never happened. For example, when hemiplegic patients with anosognosia are confronted with questions about the functioning of their paralyzed limb, they may construct memories to demonstrate against their deficit. A patient of Ramachandran does this: when asked, "Can you walk?" she replies, "Yes, I can walk; I just went to the restroom" (1996).

False memories often occur in patients with AHP alongside confabulations. Confabulations, as previously discussed, are statements or actions that are incongruent with patients' history or current situation and are held by patients to be true despite evidence to the contrary (Feinberg et al., 1994; El Haj & Larøi, 2017). Patients with AHP often use confabulations when directly questioned about their impairment. For example, when asked about their inability to move their arm, a patient responded, "I've never been very ambidextrous" (Ramachandran, 1996). Another stated, "It's just that it goes less quickly than the other one" (Babinksi, 1918). While confabulations appear to be bizarre, evidence suggests that they typically rely on a repository of true memories (Schnider, 2000). These peculiar rationalizations have led many to incorrectly attribute anosognosia to global mental confusion or an intellectual disturbance. Global mental confusion, intellectual decline, poor memory, and executive dysfunction are all commonly implicated in stroke patients, especially stroke patients exhibiting unawareness. However, these cognitive impairments are not necessary for anosognosia to occur (Starkstein, et al., 1992; Cocchini, Beschin & Della Sala, 2002; Marcel et al., 2004). It may be the case that anosognosia is the result of a higher-level cognitive deficit, but it certainly does not entail an overall impairment in intellectual ability (Turnbull, Solms & Fotopoulou, 2014).

2.2.1 Managing AHP and Its Outcomes

Once patients who have experienced stroke are stabilized, hemiplegia can be addressed with robust rehabilitation. In the hours to days following stroke onset, the primary goal is to mobilize patients with paralysis. However, patients with AHP are more likely to refuse rehabilitation for their motor impairment because it is difficult to initiate rehabilitation while patients do not accept their diagnosis, understand the need for rehabilitation, or want to participate (Diller & Gordon, 1981; Nockleby & Deaton, 1987). As a result, the rehabilitation team might spend more time convincing anosognosic patients to participate, or they may wait out patients' anosognosia, hoping it resolves within a few days. Both of these options have important long-term consequences. Once patients are stabilized, rehabilitation must be initiated as early as possible to address their paralysis (Duncan et al., 2005). A delay in initiating rehabilitation increases the length of hospital stay, and reduces functional recovery, safety behaviors, and rates of return to independent living and return to daily activities (Jenkinson, Preston & Ellis, 2011).

In addition to impeding initial access to rehabilitation, AHP can affect patients' adherence to and participation in rehabilitative programs, which may last for years following stroke onset. In the weeks following stroke onset, patients begin programs aimed at addressing their impairments and restoring function. Task-oriented practice is introduced to address patients' motor impairment. Additionally, adaptive learning, comprehension strategies, and specific rehabilitation interventions are worked into the program improve extended activities of daily living and social interaction. These occur alongside the implementation of environmental adaptations and home service. In the years following stroke onset, rehabilitation will focus on maintaining patients' physical condition

and monitoring their quality of life (Langhorne, Berhardt, & Kwakkel, 2011).[4] Good outcomes are strongly associated with patient motivation and engagement throughout these rehabilitative programs (Reker et al., 2002; Langhorne, Bernhardt, & Kwakkel, 2011). However, without patients' awareness of their mobility impairment and recognition that routine exercises and treatments, though burdensome, are likely to reduce or remove that impairment over time, it is difficult to motivate patients with AHP to engage with rehabilitation and adhere to the program over multiple months or years (Cherney, 2020). As a result, AHP may limit gains in mobility (Dobkin, 2003; Jenkinson, Preston & Ellis, 2011) and is indicative of a significantly poorer prognosis following stroke (Gialenella & Mattioli, 1992; Pederson et al., 1996).[5] Hartman-Maeir, Soroker & Katz (2001) found a significant impact of AHP on the safety level of stroke patients at discharge from in-patient rehabilitation. All patients failed to achieve full independence—a significant finding for discharge status, where patients who are unable to retain safety measures are unable to live alone. Therefore, initiating and maintaining patients with AHP' long-term rehabilitation can turn into a highly complex process full of ethical dilemmas where the issue is not just should rehabilitation be administered against a patient's will, but whether rehabilitation will be effective if administered against a patient's will, or, at least without their motivation to participate (Egbert, 2017).

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[4] Other more invasive interventions, like pharmacologic treatment, electrical stimulation, acupuncture, and biofeedback, are promising, but require further study (Dobkin, 2003).

[5] The poorer functional outcomes, while associated with access to and participation in rehabilitation programs, might also be linked to the fact that anosognosia is present with a higher frequency in more severe strokes. However, Pederson and colleagues (1996) demonstrate in their findings that patients admitted three days after stroke were more likely to be anosognosic while controlling for stroke severity.

However, it may be possible to adjust rehabilitation programs to accommodate patients' anosognosia. This may be achieved by engaging patients in rehabilitation that does not involve physical activity. For example, Ertelt and colleagues (2007) provided eight stroke patients with chronic paralysis with four weeks of action observation therapy. This type of therapy asks the patient to engage in motor imagery processes by observing daily actions, combined with physical training of the observed actions. Additionally, Fotopoulou and colleagues (2009) devised a method of improving awareness and motor function in patients with AHP using visual feedback of the patient's movements or lack thereof. Mental rehearsal has also been shown to be effective in restoring motor function in this patient group. Therefore, there are possible passive techniques that may allow those who lack the awareness to engage meaningfully in physical therapy, but these techniques require further investigation regarding their efficacy (Jenkinson, Edelstyn & Ellis, 2009; Jenkinson, Preston & Ellis, 2011). Moreover, they do not address the need to intervene in the immediate aftermath of stroke.

3.0 Informed Consent for Patients with Anosognosia

Patients irretrievably lose on average 1.9 million neurons for each minute a stroke is left untreated. As a result, the management of stroke needs to be rapidly pursued (Saver, 2006). In the field of stroke management, "time is brain"—the longer therapy is delayed, the less chance it has of being successful (Gomez, 1993). Hemorrhagic strokes are emergently treated to control bleeding in the brain, while intravenous (IV) thrombolysis (with tissue plasminogen activator) is the gold standard treatment for ischemic stroke. IV thrombolysis is used to break up blood clots and prevent new ones from forming. It is an acute treatment that should only be administered within three hours of symptom onset because of the increased risk of hemorrhage beyond three hours without a substantial proven clinical benefit (White-Bateman et al., 2007; Marsh et al., 2010; McGehrin et al., 2018; Hollist et al., 2021).[6] Other acute treatments for ischemic stroke involve medications delivered directly into the brain area affected by the stroke as opposed to through an IV injection. The time window for this treatment is slightly longer, at eight hours from symptom onset, but still limited (Clark et al., 2009). Additionally, patients with large clots can benefit from a surgical procedure to remove the clot (Catanese, Tarsia, & Fisher, 2017; Mayo Clinic, 2023). While these acute treatments might still be effective at the upper limits of their treatment windows and perhaps even beyond, the earlier they are administered, the more favorable the outcome. Marler and colleagues (2000) found that patients treated from 0 to 90 minutes after symptom onset

[6] However, this can be extended up to 4.5 hours as demonstrated by the European Cooperative Acute Stroke Study (Hacke et al., 2008; Sattin, 2022).

had better improvement at 24 hours and more favorable three-month outcomes than patients treated after 90 to 180 minutes following symptom onset.

Unfortunately, patients wait on average 1.9 hours after noticing symptoms before arriving at the hospital after a stroke and a further 0.3 hours before being assessed by a physician (Kwan, Hand, & Sandercock, 2004). Therefore, there is an average delay of 2.2 hours before patients can receive a diagnosis of stroke and be considered for treatment. This allows for a very limited window in which providers need to determine what type of stroke has occurred and how to manage it. A more recent study found that only 43.6% of patients arrived at a hospital's emergency department within 4 hours of symptom onset (Le et al., 2020). Once a patient arrives at the hospital with symptoms of a stroke, medical providers collect information from the patient about their past medical history and current symptoms. This information gathering is followed by the initiation of several assessments, which may include a physical exam, blood tests, a CT scan, MRI, carotid ultrasound, cerebral angiogram, or an echocardiogram (Mayo Clinic, 2023). Assuming these assessments and a relevant diagnosis occur within the treatment window, clinicians must seek a capacitated patient's informed consent for treatment. This process, however, moves quickly. The median time between patients' arrival at the emergency department to receiving IV thrombolysis occurred over 23 minutes. Of those minutes, 1.3 were spent providing patients with information and gaining their consent (Prick et al., 2022).

Circumstances surrounding the acute treatment for stroke provide a very small window in which patients are able to weigh their treatment options and make a decision regarding their medical care. While the goal of acute stroke management is to reduce long-term disability by preserving brain function, the therapeutic options have significant risks that must be properly considered. A systematic review, which examined a total of 5216 patients, found that thrombolytic

therapy increased the possibility of patients returning to an autonomous life following stroke, but also presented an increased risk of death (Wardlaw, del Zoppo, & Yamaguchi, 2000). The overall risk of death and disability from stroke decreases by 4% with thrombolytic therapy, but the therapy is associated with a 6% increase in the risk of both fatal and non-fatal intracranial hemorrhage.[7] The National Institute of Neurological Disorders and Stroke (NINDS) Study (1995) found that 50% of stroke patients treated within three hours of symptom onset with IV thrombolytic therapy are able to return to a completely autonomous life without any increase in risk of death at three months after stroke. This is compared to 39% of patients treated with placebo. However, the treatment group still experienced a 6% risk of developing cerebral hemorrhage in days following treatment. Cerebral hemorrhage either worsened functional outcomes by 10 fold compared to receiving no treatment in the acute setting, or hastened death in those hemorrhages that were fatal.

Due to the risk of severe harm or death that accompanies acute interventions to treat stroke or hemiplegia, it is important that patients be asked to give their informed consent to these interventions. In order to provide informed consent, patients must be able to meet the demands of the decision-making task. The damage caused by stroke may impair patients' ability to make informed decisions regarding their medical care. Anosognosia in hemiplegia (AHP) further impairs patients' decision-making abilities by preventing patients from having access to relevant information about their condition. In this section, I will argue that it is nevertheless important and possible to include patients with AHP in the decision-making process. I will begin by introducing the doctrine of informed consent and explaining why it is important. Then, I will analyze the requirement of decisional capacity in more detail.

[7] However, there is some heterogeneity in the results between studies that cannot be explained by chance alone.

Next, I will argue that both stroke and anosognosia may impair patients' decisional capacity regarding acute decisions for the treatment of their stroke or hemiplegia. As a result, many patients with AHP may not have the decisional capacity necessary to authorize or refuse treatment for their stroke or hemiplegia in the acute setting. Decision-making authority is appropriately transferred instead to a patient's surrogate decision-maker who, if possible, should make decisions according to the substituted judgment standard. This standard is preferred over the best interest principle, which would be used if surrogates lack information regarding what patients would decide if they had capacity. Because use of this substituted judgment standard is only as reliable as the knowledge of patients' values and preferences on which it is based, it is important to understand these values and preferences as accurately and completely as possible. I will demonstrate how patients with AHP may assist their surrogates in reconstructing patients' values and preferences regarding their medical care. As a result, the outcome of using the substituted judgment principle is made more reliable by engaging patients with AHP in the decision-making process. I will conclude this section by addressing some potential concerns associated with engaging patients with AHP in the decision-making process to argue that this approach serves the enduring values and preferences of patients with AHP.

3.1 The Doctrine of Informed Consent and Why It Is Important

Faden and Beauchamp (1986) distinguish two senses of informed consent: informed consent as an act of autonomous authorization, and informed consent as a norm-governed, institutionally embedded process. According to the first sense, for an act to be an informed consent, it must be an authorization that is intentional, substantially noncontrolled, and based on substantial

understanding. According to Faden and Beauchamp, substantial understanding in this first sense is understanding of the information that is material to the decision at hand. For this first sense of informed consent, Faden and Beauchamp endorse use of a subjective standard of material information that depends what an individual patient wants to know in order to make a decision. The second sense of informed consent, the institutionally embedded process of informed consent, reflects this first concept of informed consent and translates it into policy (in tort law or in institutional policies). The second sense considers what clinicians in this case must do to satisfy institutional rules. The process of informed consent has five elements—disclosure, substantial understanding, capacity,[8] voluntariness, and consent—with the first step requiring adequate disclosure of the material information. In this second, policy-oriented sense of informed consent, what is material information is determined by an objective standard—the information that a reasonable person would find relevant to the decision.

For informed consent in this policy-oriented sense to occur, capacitated individuals (i.e., those who have decisional capacity) need to receive information regarding the proposed intervention and understand that information. Generally, this includes the patient being informed of their medical condition, the recommended treatment, its associated risks and benefits, as well as the risks and benefits of alternative treatment options. The condition of substantial understanding requires that the patient understands this information and appreciates that it applies to them. Faden and Beauchamp differentiate between patients understanding what has been

[8] Capacity, which a physician may judge, is distinct from competency, which is a legal judgment (Karlawish, 2008). Faden and Beauchamp (1986), like many other authors, use 'competence' and 'capacity' or 'decisional capacity' interchangeably.

communicated and patients understanding that, in giving their consent, they have authorized a specific action. This is sometimes separated into its own element as the act of authorization, but it is also referred to as the "consent" or "decision." This is the final step in providing the second sense of informed consent and requires that an individual understands that by authorizing an intervention, the individual assumes responsibility and warrants another, their physician, to proceed. A patient may also refuse a recommended intervention. The act of consent must be made voluntarily, i.e., in the absence of a substantially controlling influence. People act voluntarily to the extent that they act without being substantially controlled by another person or a psychological force like a phobia (Beauchamp & Childress, 2001). Not all influences are controlling or ethically problematic, but only those that entirely dominate so that a person cannot act on what they will (Faden & Beauchamp, 1986).

With regard to the voluntariness of the informed consent or refusal, Faden and Beauchamp (1986) differentiate three main forms of influence: coercion, manipulation, and persuasion. Coercive influences entirely compromise an individual's ability to act according to their own will by presenting them with a credible threat of harm. The individual is unable to resist acting to avoid it. Persuasion, on the other hand, uses appeals to reason in order to induce an individual to freely accept particular beliefs as their own. Lastly, manipulation influences another's decision by altering the choices available to an individual or by altering an individual's perception of the available choices. Deception, for example, is the manipulation of information that causes an individual to believe what is false. Manipulation exists on a continuum: approaches may be more or less manipulative, and may be more or less ethically appropriate. Having someone who is trusted by a patient explain treatment options appeals to the patient's reason but also to the patient's emotions (trust, comfort). This approach may be less manipulative than if the person disclosing

information suggests that they will be very disappointed and think less of the patient if the patient were to select one option over another. Even if the information disclosed were accurate and appealed to the patient's reason, the second approach might exert substantial control over the patient's decision. If a patient's decision to authorize or refuse treatment is unduly influenced by an external or internal factor (e.g., another person or phobia), the decision cannot be said to be autonomous. Therefore, requiring that the conditions of a valid informed consent (or refusal) regarding medical treatment be met provides reasonable assurance that patients are not deceived or coerced into making a particular decision (O'Neill, 2003).

Additionally, requiring the informed consent process respects patients' ability and right of self-determination and promotes their well-being (Buchanan & Brock, 1990). Seeking and obtaining informed consent is thus valuable in two ways. First, people are more likely than others to make decisions that promote their own interests as they themselves define those interests. This is because often what best serves an individual depends on the values and goals of that individual. Requiring informed consent thus promotes patients' well-being, or rather affords them an opportunity to promote their own well-being. Moreover, people's interest in making important decisions for themselves is not based solely on this instrumental value. People generally enjoy and thus have an interest in making their own decisions, even in cases where decisions are not consistent with other interests they recognize or that may be ascribed to them, or in cases when others are better suited to make decisions to promote their well-being (Buchanan & Brock, 1990). The right of self-determination recognizes and protects individuals' interest in making decisions about their own life.

3.2 A Deeper Dive into the Requirement of Decisional Capacity

Requiring these conditions of informed consent—adequate disclosure, substantial understanding, voluntariness, and consent—seeks to enable patients to make decisions that affect their health and ultimately their well-being. In providing their informed consent for an intervention, patients accept moral responsibility for the outcome of their decision (Peterson, 2021). In order for patients to be appropriately assigned moral responsibility for important decisions regarding their medical care, patients must have decisional capacity. Patients with capacity are those whose decision-making abilities are sufficient to meet the demands of the decision-making task. Those who do not meet the decisional demands, and thus lack decisional capacity, are either unable to make a decision or the decision they make might be flawed (Buchanan & Brock, 1990). If they are allowed to make important decisions for themselves, these patients may risk serious harm and may suffer an impaired ability to make autonomous choices in the future.

Patients are judged as having decisional capacity to the extent that they possess certain abilities (Faden & Beauchamp, 1986). Patients must be able to understand their medical situation and the information disclosed to them by their provider, to appreciate the relevance of the information to their own situation, to reason about their options in light their circumstances and values, and finally, to communicate a decision (Buchanan & Brock, 1990).

The capacity to understand what has been disclosed includes possession of a broad range of linguistic, conceptual and cognitive abilities that allow patients to receive, store, and retrieve words, phrases, ideas, and sequences of information (Applebaum, 1988; Buchanan & Brock, 1990). Beyond this, patients need to be able to appreciate this information, i.e., to recognize how

what is explained applies to them and may impact their life. Capacities that contribute to patients' appreciation make it possible for patients to understand what it would be like and feel like to be in possible states and undergo various experiences; appreciation could require imaginative abilities (Buchanan & Brock, 1990; Wicclair, 1991). Reasoning and deliberation require an ability to evaluate and compare alternatives (Buchanan & Brock, 1990). Patients need to be able to draw inferences about the consequences of making a decision, engage with the likelihood of each consequence and weigh these against alternatives in order to reach a decision through a rational process (Buchanan & Brock, 1990; Grisso & Applebaum, 2006). The decision or beliefs upon which a decision is based need not be rational. It is only that the process of reasoning should follow a logical path given the beliefs that have been applied (Applebaum, 1988). The process of weighing options and their alternatives involves considering how different options and their consequences might further one's good or promote one's ends. Therefore, patients with decisional capacity require a set of values or conception of the good in order to evaluate these potential outcomes as benefits or harms to themselves and their goals. Their values should be at least minimally consistent or stable over time (Buchanan & Brock, 1990; Baerøe, 2010). Finally, patients need to possess the ability to indicate a choice and maintain that choice long enough for it to be received and implemented. This expression of a choice can occur through speaking, writing, or other behavioral means (Applebaum, 1988; Buchanan & Brock, 1990).

Decisional capacity is not a global concept applied to persons, but a concept applied to a person's ability to make a particular decision. At any one time, patients may have the capacity to make some decisions and not others. This is because the required cognitive skills and abilities are specific to the decision or task at hand (Buchanan & Brock, 1990; Peterson, 2021). As a result, it is commonly argued that the standard by which we assess decisional capacity should change in

response to the type of decision and context in which it is being made. The result is a sliding scale approach to decisional capacity, which holds that as the medical decision changes, so too should the level of decisional capacity required to make that decision (Drane, 1985; Buchanan & Brock, 1990; Owen, 2009).

Several authors argue for a risk-relative standard for decisional capacity, contending that because riskier decisions impose a greater potential threat to a patient's well-being and their future autonomy, a higher standard of decisional capacity should be required for higher-risk decisions than for low-risk decisions (Drane, 1985; Buchanan & Brock, 1990). The process of setting this standard would involve balancing a particular decision's potential risks against its expected benefits. As the potential consequences of a patient's decision becomes more serious, stricter standards for capacity should be applied (Drane, 1985; Faden & Beauchamp, 1986; Applebaum, 1988). For example, a patient who refuses a life-saving treatment should be subject to a more rigorous test of and standard for their capacity than if they accepted the recommended treatment.

If the medical intervention is not dangerous and is objectively in the patient's best interests, then a patient need only be aware of their situation to have sufficient capacity to agree to receive the intervention (Drane, 1985). Only those whose illness or injury impedes their awareness, such as those who are unconscious, cannot fulfill this most lenient standard. Drane claims that patients who deny their self or situation cannot meet this standard.

On the other hand, if the diagnosis is less than certain or treatment options are likely to be less than effective, a patient must understand the treatment options, balance the risks and benefits, and make a decision based on this understanding. Patients with severe mood and thought disorders or memory loss would not meet this standard because these patients, owing to their cognitive disorders, might lack substantial understanding of these elements. Lastly, if the proposed

intervention is high risk, a patient must be able to appreciate the implications of the medical intervention for their life. Patients who exhibit false beliefs about reality or who suffer from advanced dementia or active substance use disorders are unlikely to meet this most stringent standard for decisional capacity.

In contrast, others have argued that it is inaccurate to think that risk is what warrants a variable standard of decisional capacity (Wicclair, 1991; O'Neill, 2003). Instead, the complexity of a decision should determine which level of cognitive skills and abilities are required to meet decisional capacity. More complex decisions will require a higher level of cognitive skills and abilities, therefore a higher standard of decisional capacity. It is possible that riskier decisions are more complex decisions, but Wicclair (1991) argues that a riskier decision generates a stronger reason for making sure that a patient has decisional capacity, while a more complex decision generates a stronger standard by which decisional capacity is judged. If a patient's decision is likely to result in considerable harm toward themselves, i.e., if the risk is high, then there is more reason to make sure they are decisionally capable. However, it does not follow that a higher risk of harm should raise the standard according to which the patient is judged to have decisional capacity. Arguably, it is instead the complexity of the decision that determines this standard.

An acute stroke intervention like thrombolytic therapy carries with it the serious risk of intracranial hemorrhage, which can be a fatal consequence. According to the risk-relative standard, the decisional capacity required to authorize this intervention should be judged according to a stringent standard due to the risk of death. According to a view of decisional capacity that focuses on complexity of the decision, the assessment would be the same: the decision to authorize thrombolytic therapy demands a complex set of cognitive abilities because patients have to weigh

its serious risks and benefits in light of normative judgments about death and disability. The result is the same—a stringent standard for decisional capacity.

To further complicate the assessment of decisional capacity, an individual may have the capacity to make a decision at one time and not another (Faden & Beauchamp, 1986). For example, disease, injury, and medication can all temporarily impair decisional capacity (Wicclair, 1991; Baerøe, 2010). Even for patients not impacted by these variables, their environment and the behavior of others can have a negative effect on their level of decisional capacity (Buchanan & Brock, 1990). This is evident in hospital settings, including the emergency setting which places a high demand on patients' decisional capacities because psychological and physical stress are known to compromise patients' understanding (White-Bateman, 2007). Therefore, medical providers should, and often do their best to, remove the variables that impair patients' decisional capacity.

3.2.1 How Does Stroke Affect Capacity

Stroke is sudden, life-threatening, and becomes more serious the longer it is left untreated (Pouncey, 2019). The damage inflicted by stroke can affect patients' ability to consider their options and make informed decisions regarding their medical care (Applebaum, 2007). The degree to which decision-making is impaired varies depending on the location and size of the brain area affected by stroke (Al-Qazzaz et al., 2014; McGherin et al., 2018).[9] Owing to the complexity of

[9] Al-Qazzaz et al. (2014) provide a good summary of this interaction in Table 2 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4164290/).

the neuronal networks excited in cortical processes, stroke typically impairs more than one cognitive function (Cumming, Marshall, & Lazar, 2012; Al-Qazzaz et al., 2014).

In just less than half of all stroke patients, a decreased level of consciousness is observed (Lawrence et al., 2001).[10] These patients will not possess any of the above described abilities necessary to be judged to have decisional capacity. Of those who are conscious, cognitive impairment might still restrict their decisional capacity. Impaired cognition is estimated to occur in about 44% of stroke patients, as measured according to the Mini-Mental State Examination (MMSE) (Lawrence et al., 2001). This examination tests orientation, registration, calculation, memory, attention, comprehension, spontaneous writing, and visuo-spatial abilities (Folstein, Folstein, & McHugh, 1975; Al-Qazzaz et al., 2014). Of these, attention and executive functions are most affected at the time of diagnosis,[11] after which memory problems become more prominent and can persist three months after a stroke, but become less prevalent over time (Al-Qazzaz et al., 2014). Additionally, marked slowness of information processing is a common complaint after stroke, but is not consistent across different cognitive domains (Cumming Marshall, & Lazar,

[10] The study that produced this result included those patients who died immediately after stroke. Level of consciousness was assessed using the Glasgow Coma Scale where any score below 15 indicated impaired consciousness. However, previous studies report impaired consciousness in anywhere from 16% to 41% of stroke patients according to the investigators' definition of consciousness (Lawrence et al., 2001).

[11] Executive functions refer to a set of cognitive processes that are necessary for the cognitive control of behavior. Examples of such processes include self-control, working memory, and cognitive flexibility. From these higher executive functions are built: reasoning, problem solving, and planning (Diamond, 2013). While some of these individual processes are measured by the MMSE, the MMSE may not adequately provide a measure of executive function (Korczyn, Vakhapova & Grinberg, 2012).

2012). Given the time-sensitive nature of initiating acute treatment for stroke, this slowness is a concern for patients involving themselves in the decision-making process of informed consent for such treatment. For patients experiencing slowed thinking, reaching an informed decision while treatment is still beneficial to them might be impossible.

An impairment in any one of these areas of cognition might mean that patients cannot attend to and understand information disclosed to them or evaluate and compare their treatment options. Prick and colleagues (2022) observed stroke patients in the emergency department and then followed them to the neurology ward where they conducted structured interviews. Of the twenty patients studied, 35% felt they fulfilled all criteria for adequate decision-making—that is, understanding of information, reasoning about treatment options, understanding of consequences of the situation, and ability to communicate a choice. The majority of patients, 85%, felt they could communicate a choice. Sixty-five percent claimed to understand the information, while only 50% felt they could understand the consequences. Sixty percent considered themselves to be able to reason about their options. However, the study reports significant discrepancies between the provided and recalled information regarding the diagnosis, therapeutic options, and potential complications. While most patients were informed about their diagnosis and treatment during their hospitalization, only about half of them remembered having been informed. Among those who remembered being informed, a third perceived the information as incomplete or difficult to understand. Furthermore, five patients could not remember being treated at all. As indicated by this study, following stroke, a considerable number of patients do not fulfill the criteria for having decisional capacity for decisions regarding the treatment of their stroke or hemiplegia.

However, assessing capacities according to these broad categories might not be all that helpful. Memory, for example, is not a unitary concept. There are different types of memory—

short-term, working, episodic, semantic, and procedural memory—that are maintained by different cortical structures. Depending on the location of the stroke, one subtype of memory might be impaired, while others are preserved. Therefore, while cognitive impairments following stroke can undermine patients' decisional capacity, the extent to which they do so varies according to the type of cognitive function and the severity of the damage (Peterson, Karlawish, & Largent, 2021). As a result, decisional capacity can be thought of as occurring on a spectrum. At one end, patients have little to no impairment following their stroke and therefore retain decisional capacity. At the other end, significant cognitive impairment completely removes patients' ability to make their own decisions. Aphasia, hemineglect, and anosognosia pose unique challenges to the preservation of decisional capacity and increase the likelihood that patients who experience them lack decisional capacity to make many relevant treatment decisions (McGherin et al., 2018). Aphasia is a language production and comprehension deficit estimated to occur in 23% of stroke patients (Lawrence et al., 2001). Patients with hemineglect are unable to perceive and process stimuli on one side of their body, and therefore are unable to adequately appreciate their medical situation (McGherin et al., 2018). Hemineglect is slightly more common than aphasia, with 29% of stroke patients experiencing spatial neglect (Esposito, Shekhtman, & Chen, 2021).

3.2.2 How Does Anosognosia Affect Capacity?

How anosognosia affects decisional capacity, of course, depends on the decision to be made. Anosognosia is an independent phenomenon that is highly functionally specific (Marcel et al., 2004). A patient with AHP might be unaware of their motor impairment, while still aware of their other symptoms of stroke. In other words, anosognosia does not necessarily preclude one's awareness of one's stroke. For example, consider Mrs. FD. She is an elderly lady who had suffered

a right hemisphere stroke resulting in a complete paralysis on the left side of her body. Ramachandran (1996) describes his visit with Mrs. FD eight days after her stroke:

> **VSR**: Mrs. D, how are you feeling today?
> **FD**: I've got a headache. You know, doctor, I've had a stroke so they brought me to the hospital.
> **VSR**: Mrs. D, can you walk?
> **FD**: Yes. (FD had been in a wheelchair for the past two weeks. She cannot walk.)

While Mrs. FD is unaware of her hemiplegia, she knows that she has had a stroke and that she is being treated in the hospital. This is an important nuance to consider because capacity is decision-relative. In the acute setting, treatments are geared toward the management of stroke and, arguably, not directly the paralysis brought on by stroke. The goal is to preserve as much brain tissue as possible and also prevent complications now and in the future. As a result, one could argue that although patients are unaware of their paralysis, some patients might be aware of and can appreciate other consequences of their stroke and what it would mean to authorize or refuse treatment for their stroke. It may very well be that a patient with anosognosia can understand that they have had a stroke and that it needs to be emergently treated. Arguably, if the decision is whether or not to proceed with a treatment option for stroke, then the capacities required to make such a decision need only exist with regard to decision-making for that stroke treatment. This argument is strengthened by the fact that anosognosia does not entail an overall cognitive impairment (Turnbull, Solms & Fotopoulou, 2014).

However, awareness of hemiplegia is relevant to patients' awareness of their condition following stroke. Hemiplegia is a sequala of stroke. If a patient lacks awareness of their hemiplegia, they do not appreciate their medical condition. Though acute stroke treatments are more focused on directly preserving brain function as opposed to restoring motor movement, appreciation of one's hemiplegia is necessary to understand the impact of stroke on one's quality

of life. Without an appreciation of hemiplegia, patients with AHP are unable to judge the consequences of authorizing or refusing a treatment as those decisions apply to their current condition as well as to their future condition because hemiplegia may persist beyond acute stroke management. Therefore, awareness of one's paralysis is relevant to decisions about stroke treatment.

In their discussion of false beliefs, Faden and Beauchamp (1986) make a similar argument.[12] They claim that a false belief may impair material understanding. Borrowing from John Stuart Mill, Faden and Beauchamp (1986) discuss the case of a man who wants to cross what he believes to be an intact bridge. This belief is false because the bridge is out. Therefore, the man's understanding of his walking across the bridge is materially incomplete because it does not take into account at least one relevant description about the bridge—that if this man attempted to walk across the bridge, he would fall in the river. They go on to claim that "to the extent that a person's understanding of a proposed action is based on false beliefs about that which would otherwise be relevant to an understanding of the action, performance of that action is less than fully autonomous" (pp. 253). A decision made about a condition of which one is unaware is not an autonomous decision. As a result, many anosognosic patients should not be allowed to authorize or refuse treatment for their stroke in the acute setting.

[12] Faden and Beauchamp don't specify their argument for anosognosia. They provide the example of a patient who refuses treatment for her cancer because she was not experiencing any of the symptoms of someone who was seriously sick. She held this belief in spite of concrete evidence and her physicians' assurance. While their example better demonstrates a case of denial of illness rather than anosognosia, both conditions impair understanding in a way that is relevant to the decision at hand.

3.3 Alternatives to Requiring Informed Consent

Instead of requiring patients with AHP to provide their informed consent for treatment in the acute stroke setting, this requirement may be waived by presuming consent if the treatment is an emergency procedure, like IV thrombolytic therapy. Waiving consent has been defended on the grounds that any reasonable patient would want emergent care provided in a timely manner, and that by forgoing consent, an emergency intervention can be administered earlier, thereby averting serious harm and serving the best interests of patients (Fleck & Hayes, 2002). However, to meet the requirements for an emergency waiver of consent, the following conditions need to be met: (1) there is widely accepted and incontrovertible evidence that the emergent therapy is likely to have a positive therapeutic result, (2) delay in therapy will almost certainly have adverse or irreversible consequences, (3) there are no alternative therapies available that would be as safe and effective, and that would permit sufficient time for discussion, and (4) treating physicians are confident that reasonable persons who, given this possible circumstance to consider in advance, would agree to the therapeutic intervention and agree to forgo explicit informed consent (Fleck & Hayes, 2002).

In some studies, however, IV thrombolytic therapy produced a moderate benefit with an increased risk of intracranial hemorrhage (NINDS, 1995), and in other studies produced varied benefit with more complications (Shellinger, Fiebach, & Hacke, 2003); therefore, IV thrombolytic therapy would not meet the first condition. As a result, Fleck and Hayes (2002) argue that thrombolysis has not yet evolved into what can be considered the standard of care. Therefore, it would be ethically inappropriate to waive informed consent. Indeed, rather than waiving the requirement of informed consent, a much more rigorous standard of informed consent should be applied to the procedure because of the level of risk associated with the procedure and the likelihood that people may evaluate the relevance of that risk differently in light of their personal

values. Due to the effect of the stroke on the patient's decisional capacity, however, the patient may be incapable of participating in the informed consent process in the usual way.

3.4 Surrogate Decision-Making

When a patient is unable to give informed consent for treatment the authority to make the decision needs to be transferred to someone else (Applebaum, 2007). Buchanan and Brock (1990) propose a theory of surrogate decision-making in which several widely endorsed principles guide how decisions are to be made. These include: (i) the advance directive principle, (ii) the substituted judgment principle, and (iii) the best interest principle.

Depending on the information available and circumstance of the patient, there is typically an order to following these guidance principles. Formal guidelines for surrogate decision-making typically instruct decision-makers to appeal first to any directives issued or articulated by the patient when competent. When such directives are unavailable or insufficient given the circumstance, the second-line approach calls for decisions to be made according to substituted judgment, where those who know the patient best make decisions based on what they think the patient would have chosen if competent to do so. Lastly, if reliable substituted judgments are not feasible, decisions can be made based on the patient's best interest. The first two principles derive their justification from respect for the patient's former choices and values. The third principle, best interest, is based exclusively on others' understanding of the patient's good and is justified by the obligation to promote patient welfare (Buchanan & Brock, 1990).

3.4.1 Advance Directives

The advance directive principle states that when a "clear and bona fide advance directive is available, it is to be followed" (Buchanan & Brock, 1990, pp. 95). Advance directives are preferred over recourse to the other two principles because advance directives locate decision-making authority clearly in the formerly capacitated individual. Adhering to an individual's advance directive respects an individual's self-determination and protects them from unwanted medical treatment (Buchanan & Brock, 1990). Therefore, an advance directive takes precedence over any other guidance principle, but only if the preferences expressed are within the scope of standard of care.

There are two types of advance directives: instructional and proxy. Instructional directives allow a person to indicate which types of treatment they would wish to have or not have under certain circumstances should they become incapacitated (Buchanan & Brock, 1990). The second type is an advance directive in which an individual names someone, a proxy or surrogate decision-maker, to make decisions should the individual be unable to do so. An individual may execute both types of advance directive, and they may be used in concert, with the proxy being guided by values and preferences revealed in the instructional advance directive.

Even though stroke is a sudden event, the high frequency with which it occurs among the general public, as well as people's knowledge of its effects, make it possible for patients to take into account the possibility of suffering a stroke in their advance directives. The COAST, or Coordinating Options for Acute Stroke Therapy, directive is a stroke-specific advance directive that was developed in 2015 (Spokoyny et al.). It allows for flexibility in light of patients' medical contexts and the broader context of advances in stroke management. Patients identified as being at risk for stroke conditions can complete an advance directive like the COAST with their primary

care physician or at a stroke specialty center. It takes on average eleven minutes to complete. Should an individual then suffer a stroke and no longer have decisional capacity, the directive can quickly be translated into a medical order. This approach is promising and responsive to the time pressures associated with acute stroke management. However, the vast majority of those who lose their decisional capacity as the result of a stroke do not issue an advance directive while still decisionally capable (Buchanan & Brock, 1990). In a recent study of 143 stroke patients who died during their hospitalization, only about 30% of them had written and signed an advance directive (Alonso, Dorr, & Szabo, 2017).

If individuals do complete advance directives for stroke, they should specify their preferences regarding the management of stroke as well as the management of its sequalae, like anosognosia. Because anosognosia is less well-known and occurs in only a proportion of stroke patients, it is unlikely that, even if stroke patients do account for stroke in their advance directive, anosognosia would be included.

Furthermore, if an advance directive does exist, it runs the risk of being inapplicable—that is, the specific circumstances of the person's current state may not match those the person described at an earlier point through their directive (Friedrich et al, 2018). Due to advance directives' proactive character, it may be difficult for a patient to imagine accurately their medical condition and account for all the important decisions. Additionally, rapid and unpredictable changes in therapeutic options mean that even if at the time the directive was issued a patient was well-informed, they may not have contemplated the interventions available to them by the time the directive is used. As a result, advance directives are often either too ambiguous to cover the specific condition or its associated treatment adequately, or advance directives are too specific and still do not cover the decision at hand (Buchanan & Brock, 1990).

Moreover, reliance on advance directives assumes that patients' values and preferences do not change between issuing the advance directive and translating it for use (or such reliance ignores the possibility that they may have changed). While patients may be sure of their interests at the time they execute advance directives, these may dramatically change in unforeseen ways by the time previously issued directives are implemented (Buchanan & Brock, 1990). Studies have found, for example, that healthy external observers underestimate the quality of life those with disabilities actually report (Albrecht & Devlieger, 1999; Ubel, Loewenstein & Jepson, 2003; Kaur et al., 2015). In a survey of 714 practicing U.S. physicians across the country, about 82% of physicians reported that people with significant disability have a worse quality of life (Lezzoni et al., 2022). But research shows that persons with disability report satisfaction with the quality of their lives (Boyd et al., 1990). Goines and colleagues (2016) found that healthy observers were more likely to rate quality of life lower owing to disability than were patients with facial paralysis-related disability. Just as healthy observers inaccurately assess how their contemporaries with disabilities rate their quality of life, currently competent people may inaccurately predict how they would themselves assess their quality of life when at some future time they are in some way disabled and incompetent to make medical decisions regarding their care.

This possibility of a discrepancy in the interests and preferences of people at the time they execute their advance directives and their interests and preferences at the time those directives need to be implemented has been used to call into question whether an advance directive has moral authority at that later time. Dresser and Robertson (1989) argue that advance directives made by previously competent individuals should not be applied in their now incompetent state because the interests of the currently incompetent individual may differ substantially from the interests of the previously competent individual, or those that the previously competent individual anticipated

having when in the current state. Indeed, they argue, those issuing an advance directive have no way of knowing what their interests would be once they are in a state of incompetence. Allowing the past preferences of a previously competent individual to apply to their now incompetent state might allow insufficient or mistaken information to guide medical decision-making. As a result, incompetent patients are not protected from unwanted medical care and their right to self-determination is not respected.

3.4.2 Substituted Judgment and Best Interest Principles

Surrogate decision-makers may be named in a patient's advance directive, or may be identified, according to law or institutional policy, based on their degree of relationship to the patient or their knowledge of the patient's values and preferences. There are two principles according to which a surrogate can make a decision on behalf of the patient: the substituted judgment principle or the best interest principle. According to the substituted judgment principle, surrogates make decisions based on what the patient would choose if they had decisional capacity and were aware of the relevant facts of their case. The instrumental value of self-determination is preserved, although indirectly, by choosing the decision that best aligns with a person's values and preferences when they had capacity (Buchanan & Brock, 1990).

However, substituted judgment is difficult to implement. Even if surrogates are willing to decide on a patient's behalf, they may be subject to the same time pressures that constrain patients' own decision-making. Additionally, implementation of the substituted judgment principle runs into many of the same issues as those expressed above about advance directives. In order for a surrogate to use substituted judgment, the patient must have expressed relevant preferences prior to becoming incapacitated. Many individuals do not do this, and if they do, they may have

expressed contradictory preferences or preferences that are too broad to guide the surrogate in their decision-making (Buchanan & Brock, 1990). Studies show that in the absence of previous discussion between a patient and their proxy, the proxy's ability to predict what the patient would want is poor (Seckler et al., 1991) or even no better than chance (Suhl et al., 1994). However, it is also not clear that previous discussion improves surrogates' predictive accuracy. Shalowitz et al (2006) report that neither patient designation of their surrogate nor prior discussions of patients' preferences improved surrogates' predictive accuracy (judged according to how well surrogates' decisions matched patients' decisions). In this study, surrogates were least accurate in scenarios involving stroke, where they were only slightly better than chance at 58% accurate (Shalowitz, 2006).

Setting aside concerns raised by Dresser and Robertson, it is generally accepted that the relevance or appropriate use of the substituted judgment principle varies according to the strength of the evidence of patients' values and preferences, the evidence on which the decision is based (Buchanan & Brock, 1990). The more specific the preference expressed by the patient previously, the greater its evidential weight. The more frequently a preference was expressed previously by a patient, the greater its evidential weight. And lastly, the more sources of evidence, the stronger the evidential base (Buchanan & Brock, 1990). To the extent that the surrogate lacks knowledge about the patient's values and preferences, then the best interest principle should take precedence over substituted judgment.

The best interest principle asks a surrogate to determine what will best serve the patient's interests. Interests may be objectively ascribed, while preferences are personal, subjective, and particular to the patient. According to the best interest principle, the treatment option with the greatest net potential benefit should be selected in order to maximally promote the patient's well-

being as determined without specific knowledge of the patient's values and preferences (Dresser & Robertson, 1989; Buchanan & Brock, 1990). However, as Buchanan and Brock argue, the substituted judgment and best interest principles cannot so easily be separated in their application. It may be that a surrogate has knowledge of the patient's values and preferences, but this knowledge is based on relatively weak evidence of what the patient would want. The surrogate can apply that knowledge, but within the limits of the basic interest principle.

Whether the substituted judgment or best interest principle is used, there is often a reluctance on the part of proxy decision-makers to participate in the consent process, perhaps owing to the anxiety about making an important decision for someone else, especially when that decision brings with it the risk of life-long disability or even death (White-Bateman et al., 2007). An Italian survey of 685 people and their families found that 84% of people would want a family member to decide for them should they have a stroke and not have decisional capacity (Ciccone, 2001). However, only 41% of family members felt they would be able to decide on another member's behalf.

These difficulties associated with surrogate decision-making in the context of stroke are compounded by the complexity of the decision at hand and its normative character, specifically to the need to balance the risk of death against the risk of life with disability. Some acute treatments for stroke or hemiplegia improve functional outcomes for patients following a stroke, but with significant risks to consider. Thrombolytic therapy, for example, can substantially benefit a patient in the long-term, but it involves immediate risks possibly leading to death. Patients may avoid more severe disability or death by receiving thrombolytic treatment, but expose themselves to serious risks, like cerebral hemorrhage, that might still result in severe disability or death. If cerebral hemorrhage does not occur, patients generally have better functional outcomes from

receiving thrombolytic therapy; however, some disability might remain that might be more undesirable to patients than the possibility of death when forgoing treatment.

Many patients' decisions depend on how they weigh death against disability. In the Italian survey study mentioned earlier, 59% of responders would prefer to risk dying by accepting thrombolytic treatment rather than accept the likelihood of living severely disabled if no treatment is pursued. A further 22% of responders were unsure of what they would decide. In this context, as in all contexts, deciding whether to authorize or refuse treatment involves a value judgment (Cocchini et al., 2001); however, it may be especially difficult to know what the stroke patient would want because so much uncertainty surrounds how people trade-off the risks of death and disability.

3.5 Improving Surrogate Decision-Making by Engaging Patients in the Process

Typically, the patient's values enter a process of shared decision-making that requires careful discussion between the patient, their medical provider, and perhaps the patient's friends or family. In the most ideal scenario, hemiplegic patients have sufficient cognitive abilities to be able to use the information disclosed to them by their provider to make an informed, voluntary decision about whether or not to proceed with the recommended treatment for their stroke or hemiplegia. This is ideal because patients are able to weigh their options in light of their current values and preferences. However, stroke can impair patients' decision-making capacity, especially in the acute setting. Therefore, in the acute setting decisional authority often falls to stroke patients' proxies. If this is the case, advance care planning can provide evidence of patients' values and preferences, but cannot reflect possible evolution of patient values and preferences, and may not

be interpretable with regard to current treatment options or standards of care. Proxies are charged with the difficult job of reconstructing patient preferences, if possible, even though these reconstructed preferences may not accurately reflect the current values and preferences of patients.

Anosognosia may complicate medical decision-making for stroke patients in three ways. First, it likely necessitates the use of a surrogate decision-maker, because anosognosia may prevent patients from accurately appreciating their current medical condition and predictions of their future quality of life. Patients may thus be incapable of making their own informed treatment decisions. Second, when a surrogate makes a decision on behalf of the patient, the surrogate may have to contend with the patient's active dissent from the treatment regimen that the surrogate chooses. Surrogates may feel less confident about what the patient would want if competent, or about what serves patients' interests best, because the surrogate must reconcile previously expressed wishes with what the patient is saying in their current anosognosic state. Third, patients may experience negative effects that are contrary to their interests. Patients may experience significant harm as a result of being excluded from taking part in their own medical decisions when they are aware of their exclusion yet cannot appreciate the reason for such exclusion. Acting in a way to which patients actively dissent or with which they actively disagree may lead patients, and even their surrogates, to experience depression, frustration, and anger. In addition to being a negative life experience in itself, experiencing these emotions might also exacerbate the effects of the neuropathology already in existence, making the patient even more debilitated (Peterson, Karlawish, & Largent, 2021).[13] Moreover, the patient's dissent or lack of concurrence with a treatment plan may undermine the treatment's potential benefit.

[13] This is often seen in caring for patients with severe dementia (Smebye, Kirkevold, & Engedal, 2012).

Depriving patients of the opportunity to make their own medical decisions is a sufficiently serious ethical concern that we want to do our best to avoid it or ensure that it is warranted by protection of their other important interests. There is, therefore, an obligation to maximize patients' capacities in order to allow them to make their own decisions if at all possible. This obligation is uncontroversial. Patients with mild dementia are often assessed for their competence early in the day to avoid assessment while they are experiencing sundowning. Additionally, if time allows, medical providers can identify and correct treatable conditions that might impair an individual's decisional capacity—for example, by reducing sedation, or treating anxiety, depression, or fever—before asking patients to make an important decision about their medical care (Applebaum, 2010).

As has been established, stroke patients might not retain the cognitive abilities necessary to make their own medical decisions. Anosognosia represents a further reduction in those cognitive abilities because it impairs patients' ability to appreciate their hemiplegia. As a result, treatment decisions these patients make may not incorporate and weigh the serious consequence of their hemiplegia. Nevertheless, while anosognosic patients may not meet the demands of decisional capacity, they may retain some of the cognitive abilities that support decision-making (Peterson, Karlawish, & Largent, 2021). Anosognosic patients may be able to understand that they have had a stroke, that it needs to be emergently treated, that treatment carries with it particular risks, and communicate their values and interests. Therefore, it would be potentially harmful and disrespectful to fail to involve stroke patients in acute decision-making about their care when they may be able to participate to some degree. Moreover, a considerable number of patients with stroke actually want to be actively involved in decision-making in the acute setting (Prick et al., 2022).

3.5.1 Involving Patients with AHP through Supported Decision-Making

Although they lack awareness and understanding of important information relevant to predicting their quality of life, patients with AHP may be able to contribute to decisions to treat their stroke or hemiplegia in the acute setting. It would be ethically desirable to do so, because treatment decisions in which they are involved may more reliably reflect their contemporaneous view of their interests. To understand how to achieve this involvement, it is useful to consider a potentially analogous situation: for patients with intellectual or developmental disabilities, there is growing interest in what is called "supported decision-making." Patients use their surrogates as "cognitive prostheses" in order to enable them to make their own decisions. Supported decision-making occurs when a patient with impaired capacity freely enters into an agreement with their proxy who assists the patient in exercising self-determination (American Bar Association, 2017). It is used for adults with cognitive disabilities that place them at the "margins of autonomy" (Peterson, Karlawish, & Largent, 2021). The patient "outsources" whatever cognitive and functional capacities cannot be completed "in house," but retains the authority to make decisions: the patient, not their surrogate, makes the decisions. For example, someone with a memory impairment might rely on their proxy to take notes and remind them of the information at a later point. The patient transfers the capacity for memory to someone else. The patient can then rely on that source to assist them in their decision-making. Supported decision-making is not necessarily something new; many patients ask their friends and family to accompany them to an appointment to ask questions, take notes, guide decisions, and provide emotional support (Blumenthal-Barby & Ubel, 2021). The benefit of this approach for individuals with some but insufficient cognitive abilities is that it strikes a balance between respecting individuals and their interest in self-determination and protecting vulnerable individuals' welfare. A similar approach to decision-

making for patients with AHP might be pursued, so that their lack of some capacities does not completely remove them from participating in medical decision-making. At the same time, they would need to be protected from making potentially harmful decisions they would not otherwise make if they were not anosognosic.

The supported decision-making approach would have to be adjusted in a few ways to benefit stroke patients with anosognosia, because the ability to appreciate one's condition cannot be out-sourced as effectively as some other cognitive abilities like memory. In supported decision-making for adults with cognitive disabilities, the patient transfers responsibility for exercise of a particular capacity—for example, the capacity for memory or for complicated, abstract reasoning—to someone else. The patient can then rely on that source to assist them in their decision-making through the exercise of that capacity. In contrast to abstract understanding or memory, appreciation involves understanding that something applies to oneself and evaluation of risks or circumstances in light of one's personal values and preferences. The ability to appreciate hemiplegia—and, in turn, its relevance for judgment about quality of life and implications for medical decision-making—inherently relies on an individual's experience of hemiplegia. The exercise of the capacity for appreciation cannot be readily transferred to someone else. Therefore, it does not seem possible for supported decision-making to enable patients with AHP to retain decision-making authority for the acute management of stroke when these patients cannot appreciate their condition.

Nevertheless, though patients with AHP may fail to appreciate the experience and implications of paralysis of a limb, patients may retain specialized knowledge of their values and preferences. If a surrogate could obtain that knowledge of the patient's values and preferences and use that knowledge to weigh treatment options relevant to the patient's current condition (including

the stroke, the paralysis and other stroke sequalae, risks and benefits of potential treatments, and so on), the surrogate could employ the substituted judgment standard for surrogate decision-making. The surrogate could obtain this knowledge by asking the patient about their values, preferences, and views about the patient's condition, though perhaps in a more abstract way, given that the patient with AHP specifically does not appreciate that some of those conditions (e.g., paralysis) actually apply. By involving the patient in their current state in surrogate decision-making, the strength of the evidential base for such decision-making is increased. As a result, the surrogate decision-maker would be assisted in reconstructing the patient's values and preferences, and the outcome of using the substituted judgment principle would be more reliable.

To enable a surrogate to obtain this knowledge, it might be possible to ask the patient to consider a hypothetical scenario. The patient might imagine they have had a stroke resulting in deficits similar to those they are currently manifesting. Essentially, the patient would be asked to issue an advance directive about a condition-treatment dyad which applies to their current situation, but of which they are currently unaware because of their anosognosia.[14] The hypothetical scenario should provide the patient with two layers of information: one layer concerns information relevant to the patient's condition following stroke (e.g., their paralysis) and the available acute treatment options. A second layer would include information relevant to the patient's anosognosia. After providing the patient with the relevant information regarding their hypothetical stroke and its treatment, the patient would be asked whether they would authorize or refuse the recommended treatment option given the facts of the hypothetical scenario. If the patient's response is to refuse

[14] Worrall (2005) followed a similar protocol and reported its success. Unfortunately, the author does not elaborate on how this success is quantified.

treatment in the hypothetical scenario, then they should be prompted to explain how they reached such a decision. If, however, the patient's response is to authorize treatment in the hypothetical scenario, they could be prompted further to consider whether their answer would change if in the hypothetical scenario they were not aware of their paralysis. The reason for this additional line of questioning is that a lack of awareness of one's condition is likely to result in the patient's dissent regarding treatment until such time as they regain awareness. Being treated against one's active refusal may be enough reason for a patient to refuse treatment in the hypothetical decision context, even if the patient believes a particular treatment would be in their best interests and in accordance with their values. The patient might, for example, hold self-determination or "the right to choose" to be of such overriding importance as a value that being treated in a way contrary to their expressed preference, even (or perhaps especially) for paternalistic reasons, may be abhorrent to them.

Therefore, in employing the hypothetical scenario, patients should be given a chance to weigh this information about the possibility of anosognosia or active dissent so that surrogates can be confident of the patients' values and preferences. Patients who authorize treatment in both hypothetical scenarios present a clear view of their interests. Patients who authorize treatment in the first hypothetical scenario, but refuse treatment when the patient is informed that they would be unaware of their hemiplegia and the need for treatment should be prompted further to explain how they reached such a decision with the goal of this exercise being to get to the core of patients' enduring values.

3.6 Addressing Potential Concerns

3.6.1 Deception

It might be objected that the use of such a hypothetical in a modified form of supported decision-making is deceptive. The material implications of the patient's response are indeed different from what they are led to believe: their surrogate will use the patient's response to guide a real, not hypothetical, action. This is not, however, a case of ethically problematic deception. Deception is ethically problematic because it intentionally causes a change in an individual's beliefs with the result that the individual's autonomy is undermined. Deception in medicine is generally wrong because it undermines patients' autonomy and breaks down the trust between medical providers and their patients. Engaging patients in the proposed hypothetical exercise, on the other hand, may be an effective way to discover patients' contemporaneous value system and learn what kind of treatment, if any, they would want given the relevant facts of their current circumstance. It would have the potential to respect their individual preferences and may be seen by the patients themselves, at least in the longer-term, to respect their autonomy or at least to promote their interests in light of their personal values and preferences.

3.6.2 Tailored Responses

Of course, patients may suspect that their response to the hypothetical exercise will be used to guide a real treatment decision, particularly if the hypothetical scenario reflects aspects about patients' condition of which they are experientially aware, or if patients have been queried about the condition about which they are experiencing anosognosia and then that condition appears in

the hypothetical scenario they are asked to contemplate. Anosognosic patients may then suspect that their response will be used in a way that they may perceive as being contrary to their beliefs or interests. These patients may then be reluctant to respond or might tailor their response so that when applied to their current circumstance will not conflict with what patients believe to be true in their anosognosic state. As a result, the strength of the evidential base would be unchanged or the evidence made complicated for the surrogate to interpret.

However, recall that AHP is not a mere ignorance of paralysis; it is an obstinate determination not to recognize or acknowledge paralysis. As a result, any attention drawn to the impairment is typically quickly redirected and its memory suppressed. Patients with AHP are unlikely to remember attention being drawn to their paralyzed limbs, and if they do, they might remember there being no issue in moving them. Therefore, anosognosic patients engaged in a hypothetical exercise might not realize they are being manipulated into providing their view of their interests because these patients might not remember previous attempts to induce their awareness of their hemiplegia.

When faced with the hypothetical situation, the patient may be able to acknowledge hemiplegia from a more removed position. Marcel and colleagues (2004) conducted experiments concerning how patients with AHP estimate their abilities in the first person as compared to the third person. The authors found that patients with AHP gave less accurate estimates of their bimanual abilities when asked, “How well would you be able to do this task in your present state?” than when they were asked, “How well would the examiner be able to do this task if he was in your state?” Therefore, patients with AHP demonstrated awareness of the relevance of a disability depending on whether the disability was applied to them or presented abstractly. Some patients even admitted to their paralysis if they were asked in a manner that treated the limb as a separate

agent. For example, to the question, “Is [your arm] ever naughty? Does [your arm] ever not do what you want?” five patients were able to acknowledge the inability of their arm to move.

These results not only demonstrate how a hypothetical exercise may be used with patients with AHP to engage with their values and preferences about disability, but also suggest there might be possible alternative methods to doing so. If asking patients to engage in an imaginative exercise about themselves generates unnecessary distress for them, perhaps because the account of the impairment is not sufficiently abstract or removed from their actual situation, then it may be possible to elicit patients’ values and preferences by asking them to consider a hypothetical situation about someone else who has suffered a stroke with deficits similar to those manifested in the patient.

3.6.3 Ability to Determine Patients’ True View of Their Interests

One might argue that a patient’s response to what appears to them to be a hypothetical scenario might not reflect their true preferences if they were aware of their hemiplegia or anosognosia. However, there is reason to believe that patients’ response in their hemiplegic state, even when anosognosia is present, may more accurately reflect their preferences than would their previously expressed preferences (those expressed prior to the onset of hemiplegia), because their contemporaneously expressed preferences are more informed by the experience of hemiplegia.

Even though patients with AHP might explicitly deny their current state of paralysis, it does not necessarily follow that they do not have access to experience of their paralysis. Awareness exists on a sliding scale such that one can demonstrate partial awareness of their deficit (Schacter & Prigatano, 1991). While patients with AHP might not explicitly acknowledge their deficit, they may still behave in a way that is consistent with knowledge of their deficit because they might be

unconsciously processing some aspects of their deficit (Ramachandran, 1996; Fotopoulou et al., 2010; Cocchini et al., 2010). In their previously capacitated state, having never experienced a motor disability, patients with AHP might have strong preferences concerning how to weigh death and disability according to their interests. However, because at a deeper level of consciousness patients with AHP may know what it feels like to have hemiplegia, this implicit knowledge may unknowingly cause them to adjust how they weigh disability against death. Because patients in their hemiplegic state may now have access to evidence concerning what it would be like to live with a disability, even if that evidence is processed implicitly, the contemporaneously expressed preferences of patients with AHP might more accurately reflect their true, informed preferences.

Dresser and Robertson (1989) similarly argue that the values and preferences of previously capacitated individuals should not be applied to their treatment in their now incapacitated state because, as the evidence suggests, people are poor at predicting their interests in a state that they have not experienced (Albrecht & Devliger, 1999). However, Dresser and Robertson's view seems relevant only when the current person is going to be the person to whom the decision or preference is applied. AHP is typically a temporary incapacity. A preference expressed by patients with AHP in their current anosognosic state will not only apply to patients with AHP in their current anosognosic state, but also to these patients in their future non-anosognosic state once they regain awareness of their hemiplegia. The future non-anosognosic state is closer to patients' previous non-anosognosic state prior to the onset of stroke and hemiplegia. Therefore, it might seem that the preferences of patients' in their previous non-anosognosic state should be given priority over their current preferences regarding what is only a temporary state.

However, the state of interest for decision-making in the acute setting following stroke—the state that is relevant to their preferences concerning disability—is the hemiplegic state and not

the anosognosic state. Whether or not patients with AHP receive emergency treatment for their stroke or hemiplegia, motor recovery and the reduction of the impact of disability occurs over many months, if it occurs at all. Ability to walk, for example, is not recovered in many stroke patients by the six-month mark (Lord et al., 2004; Coupar et al., 2011; Kwakkel & Kollen, 2013). Because patients with AHP will have to deal with some degree of disability or weakness well beyond the acute stage, and well beyond the return of their awareness of their motor impairment, patients with AHP in their hemiplegic state are more similar to their future contemporaries than persons pre-stroke. The goal of engaging patients with AHP in a hypothetical exercise is to determine their current view of their interests, which might now be informed by their experience of hemiplegia even if patients are not consciously aware that this is the case. Those interests will likely reflect patients' long-term view of their interests as persons with some degree of disability. This possibility of implicit knowledge of one's mobility impairment might actually be a reason to favor the use of a hypothetical scenario to glean information from patients for use in surrogate decision-making, rather than a more typical approach of employing an advance directive or relying on previously expressed preferences to guide surrogate decision-making.

3.6.4 Patient Perceptions

While this approach may more reliably discover patient's actual (current and future) values and preferences than relying on previously expressed preferences, a decision that authorizes treatment related to stroke or hemiplegia might be perceived by the patient as contrary to what they would want. As previously mentioned, AHP increases the likelihood that patients will refuse treatment that draws attention to their disability even if treatment aligns with their actual, non-anosognosia-based preferences. The hypothetical exercise may allow proxies to feel more

confident about knowing the patients' actual values and preferences, but patients may feel that their preferences are being ignored. Whether a treatment decision is close to, or even exactly, what the patient would want if they were able to appreciate the condition about which they are anosognosic may not have an effect on whether the patient nevertheless believes that their right of self-determination is not being respected. Because people generally enjoy and thus have an interest in making decisions for themselves, patients with AHP may be, at least temporarily, psychologically harmed by their surrogates' decisions even if these decisions promote the instrumental value of self-determination. There may be no way to avoid this harm in the context of anosognosia. However, increasing the strength of the evidential base for surrogates' decision-making is nevertheless advantageous because it allows proxies to serve the values of anosognosic subjects and thereby respect them as persons even while acting contrary to their expressed, albeit distorted anosognosia-based, preferences.

4.0 Informed Consent for Prospective Research Subjects with Anosognosia

Over the past thirty years, and through many iterative research trials, thrombolytic and endovascular therapies, among other non-standard therapies, have been developed to treat stroke in the acute setting (Muir & Saposnik, 2022). However, current therapies have strictly limited indications. Even when administered within these limits, current therapies are associated with severe, and sometimes fatal, risks. The seriousness of these considerations steers the field toward developing more effective and safer alternative therapies. While ongoing research aims to mitigate the shortcomings of current therapies (Muir, 2021; Menon et al., 2022), there is growing interest in developing alternative technology and techniques to improve early detection, stroke classification, and drug delivery (Sarmah et al., 2017). Much research is still to be done to achieve this goal.

Furthermore, while advances in the past few decades have led to improved understanding of stroke and its management, some of its sequalae, like anosognosia, are less well understood. Studying and understanding anosognosia is necessary to develop treatment options, while also contributing to researchers' understanding of higher cognitive functions, and indeed consciousness more broadly (Pia et al., 2004). However, a standard treatment for anosognosia has yet to be proposed. Therefore, patients with anosognosia in hemiplegia (AHP) need to be enrolled in research trials that study either important aspects of stroke, hemiplegia, and/or anosognosia, or the outcome of potential therapeutic interventions aimed at treating these conditions.

In order for individuals to be enrolled in research as subjects,[15] generally they must provide their voluntary, informed consent. This would be true of patients with AHP. As I have argued in the previous section, however, having anosognosia complicates—both practically and ethically—the process of providing informed consent. Obtaining informed consent from patients with AHP is even more complicated in the context of research than in clinical care. This section will explain why this is so, and elucidate why patients with AHP need to be approached cautiously to enroll as subjects in research studies.

In this section, I will consider how anosognosia challenges the ethical requirements of research. I will begin by examining how informed consent to research is different from informed consent to treatment. Then, I will argue that it is preferable for patients with AHP to nevertheless be enrolled as subjects in research via their surrogate decision-makers than to omit them from research altogether. Due to the nature of research, surrogate decision-making to enroll those who lack decisional capacity occurs in accordance with safeguards designed to protect vulnerable

[15] Various terms can be used to describe individuals who participate in research according to the type of research. The NBAC (2001) lists in addition to 'subjects', "respondents, observed, interviewees, informants, participants and volunteers" (p. 33). For the purposes of this thesis, 'subjects' is a more appropriate term that is used to describe participants enrolled in clinical research who are subjected to an action. I will use it here in the context of anosognosic patients enrolled in research because it specifically highlights the power dynamic between the individuals enrolled in research and those conducting the research. It is important to note, however, that some individuals who participate in research find the term 'subject' offensive and consider it to dehumanize these individuals. In response, many organizations, including the NBAC (2001) have transitioned to using the term 'participants' to be more respectful of individuals who participate in research and to emphasize their active not passive role. While I agree with this adjustment, for this discussion of vulnerable, incapacitated patient-subjects, it is important, I think, to keep the spotlight on their vulnerabilities and their risk of exploitation.

research subjects. These safeguards can restrict potential subjects with AHP from accessing the potential benefits of research participation. They can also prevent or restrict research that might benefit others. I will demonstrate how, by employing the approach described in section two, it is possible to engage potential subjects with AHP in the decision-making process to allow them to be enrolled in research. I will argue that they may be enrolled even in research with a greater than minimal risk of harm, if such enrollment is in line with subjects' values and preferences not altered by false, anosognosia-based beliefs. Employing the approach described in section two respects the values and interests of decisionally incapable subjects while protecting them from undue harm. I will conclude by addressing some limitations to applying this approach in the research context.

4.1 How Research Differs, Ethically, from Clinical Care

Participating in research is different from receiving clinical treatment, which is intended to benefit an individual patient. By contrast, the primary goal of research is producing generalizable knowledge and not benefitting an individual subject even though the subject may benefit from components of a research trial (Pouncey & Merz, 2019). As a result, research has the potential to exploit its subjects because it exposes them to a risk of harm for the benefit of others (Berg, 1996; Emmanuel, Wendler, & Gerdy, 2000).

4.1.1 Types of Research

Different types of research expose research subjects to different levels of benefit and harm. In research, 'benefit' describes something of a "positive value related to health or welfare"

(Belmont Report, 1979, p. 8). Participation in a research study may benefit its subjects both directly, indirectly, or both. Direct benefits are therapeutic benefits to research subjects that directly result from them receiving an experimental intervention (Deshpande et al., 2020). Research trials that provide the prospect of direct benefit in at least one component of the study are referred to as 'therapeutic research' because these types of research have therapeutic potential (NBAC, 2001). However, no research study as a whole can be accurately classified as therapeutic research because the therapeutic component is still under investigation, and the purpose of research is to acquire knowledge, specifically to learn whether the hoped benefit is reliably achieved (NBAC, 2001). Due to the experimental nature of research, research subjects cannot have a reasonable expectation of success. However, participation in some research studies might provide a direct benefit to research subjects.

Clinical research exposes research subjects to experimental interventions involving medical drugs and devices that go through several phases to test their safety, determine their effectiveness, and identify risks. There are typically three phases of clinical trials that are conducted before a drug or device can be approved for clinical use in humans. Phase I clinical trials attempt to establish the safety of new drug or device, including testing for an agent's toxicity and side effects. This phase of study typically holds the prospect of little or no direct benefit to research subjects. Phase II clinical trials continue to assess safety and also seek to determine the effectiveness of a new drug or device for a particular medical condition (NIH NIA, 2023; University of Cincinnati College of Medicine, 2023). Some phase II trials are randomized controlled trials (RCTs). Finally, phase III clinical trials gather additional information about a new drug or device's safety and effectiveness, comparing different dosages of drugs and comparing the intervention with other approaches to treatment before it can be approved for use in the clinical

context (NIH NIA, 2023; University of Cincinnati College of Medicine, 2023). Here RCTs are the gold standard. RCTs compare experimental treatment to the untreated progression of an illness under investigation, or compare different treatments (sometimes against placebo), by randomly sorting research subjects into two groups (Nardini, 2014). RCTs, because they involve the administration of a new treatment, risk exposing research subjects to increased harms or burdens, but subjects may directly benefit from participating if they receive an active treatment and the treatment proves beneficial (University of Cincinnati College of Medicine, 2023).

Subjects may also receive indirect benefits from participating in research. Indirect benefits are those that result from "mere participation in the study" (Deshpande et al., 2020, p. 95). Increased feelings of altruism, access to increased medical attention, or compensation for research participation can all provide an indirect benefit to subjects simply because subjects are enrolled in a study, even when the study does not result in direct benefit, (Deshpande et al., 2020; NBAC, 2001). Research trials that result in only indirect benefits are often categorized as involving 'non-therapeutic' components (National Commission, 1975). Observational studies are an example of a non-therapeutic research design. Observational studies are those in which the investigator does not act on or interact with research subjects, but instead observes the natural relationships between factors and outcomes (Thiese, 2014). Though observational studies do not afford subjects to a prospect of therapeutic benefit, subjects can nevertheless benefit indirectly from their participation if they value being altruistic, they receive compensation or access to diagnostic texting, and so on.

Both therapeutic and non-therapeutic research trials can expose research subjects to the risk of harm or burden as a result of participating in research. 'Risk' of harm refers to both the chance of experiencing a harm (its probability) and its magnitude (its severity) (Belmont, 1979; NBAC, 2001). The NBAC (2001) broadly categorizes harms as "physical, psychological, social,

economic, legal, or dignitary" (p. 71). Physical harms include "injury, illness, pain, suffering, or discomfort", while psychological harms include "the research participant's negative perception of self, emotional suffering, or aberrations in thought or behavior" (NBAC, 2001, p. 71). Dignitary harms are those "incurred when individuals are not treated as persons with their own values, preferences, and commitments, but rather as mere means, not deserving of respect" (NBAC, 2001, p. 72). The likelihood of harm runs from very low to high, while the severity of harm runs from trivial to fatal (NBAC, 2001). Typically, research is classified as involving either minimal risk or greater than minimal risk (NBAC, 2001). These categories are somewhat vague leading to difficulties in interpretation. For example, federal regulations define minimal risk research as research in which "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (45 CFR § 46.102(j)). The 'daily life' considered relevant for purpose of comparison is that of the healthy general population, not that of research participants, vulnerable populations, or unhealthy individuals (NBAC, 2001).

4.1.2 Ethical Requirements of Human Subjects Research

An aim of ethical requirements for conducting human subjects research is to protect subjects from harm. In determining whether a particular research study presents an acceptable level of risk of harm, that risk is to be weighed against, and found to be outweighed by, the social value of the research and its potential benefit to research subjects. The Nuremberg Code (1947), the

Declaration of Helsinki (revised 1996), the Belmont Report (1979), and other similar reports[16] have guided the ethical conduct of human subjects research for the past seventy years. The Belmont Report (1979) names three basic ethical values for conducting clinical research: respect for persons, beneficence, and justice. The principle of respect for persons requires that subjects be treated as autonomous agents, and that subjects with diminished autonomy be protected from the potential harms of research. The principle of beneficence seeks to protect subjects from harm and promotes their well-being. According to this principle, research should be structured to minimize possible harms to research subjects. Finally, the principle of justice demands that the potential benefits and risks of research be distributed fairly according to the principle of justice. This means that no one group should receive disproportionate benefits or bear disproportionate harms or burdens from research. The principle of justice applies to classes of people rather than to individuals.

To promote these basic ethical values, ethical frameworks for conducting research have been developed. Emmanuel, Wendler, and Gerdy (2000) identify seven requirements that form a coherent framework for determining whether a particular clinical research project or protocol is ethical. The authors argue that to be ethical, clinical research must have the potential to generate valuable knowledge and be conducted in a methodologically rigorous manner. Subjects should be recruited according to the scientific aims of the research and the fair distribution of potential risks and benefits of research participation, then enrolled only following their voluntary, informed consent. The potential risks to each enrolled subject must be minimized, while enhancing the

[16] Emmanuel, Wendler, & Gerdy (2000) provide a comprehensive list and summary of the relevant reports in their Table 1.

potential benefits, but the sum of the potential benefits to individual subjects and society must outweigh or be proportionate to the risks. Once enrolled, subjects must be permitted to withdraw their participation, have their privacy and welfare protected, and be kept informed of the research and its results. The extent to which a research project meets these requirements should be reviewed by individuals unaffiliated with the research group or institution.

4.2 The Requirements of Informed Consent for Research

Informed consent to research respects research subjects' capacity for and right of self-determination and enables them to protect their well-being insofar as it is assumed that people are the best judges of what is good for them (Karlawish et al., 2008; Deshpande et al., 2020; Faris et al., 2022). While the ethical value of this requirement should now be familiar, informed consent to research differs from its value established in the previous discussion concerning clinical treatment, because the goals of research are different from that of clinical treatment (Vaishnav & Chiong, 2019). The goal of clinical treatment is to benefit individual patients. In contrast, research is not designed primarily for the benefit of its subjects. While often exposing subjects to risks and burdens associated with their participation, clinical research has the goal of generating generalizable knowledge to address health concerns, increase our understanding of human biology, or both. Capacitated individuals are permitted to consent to research even though it is not designed to benefit them directly, if the risks and burdens of participation fall within an acceptable range (Moreno, 2001). Allowing prospective subjects to decide whether to participate in a research trial only after having assessed the expected risks and benefits associated with research participation protects prospective subjects from undue risk of harm (Wicclair, 1993).

In order to have the capacity to provide consent to participate in a research study, a prospective subject must be able to understand the information disclosed to them, appreciate the potential risks, burdens, and benefits involved, reason and deliberate about their decision, make a decision in light of their own values and preferences, and communicate that decision (Deshpande et al., 2020). However, the capacity requirements for some research enrollment decisions might involve a higher threshold than decisions to consent to recommended clinical care. The Common Rule (2018) requires the following information be provided to each subject: 1) the study's aim, methods, and expected duration of the subject's participation, 2) any reasonably foreseeable risks or burdens to the subject, 3) any reasonably expected benefits to the subject or others, 4) appropriate alternative procedures or treatments, 5) plans for use of information, 6) the management of adverse events, 7) who to contact regarding questions or adverse events, and 8) the voluntariness of participation and options to withdraw (45 CFR 46.116). As a result, there is more for potential research subjects to understand from disclosures for participation in research than from disclosures for clinical treatment, which might necessitate a more stringent standard of capacity according to the task-relative standard of decisional capacity (Wicclair, 1991). Within a few hours of symptom onset, prospective subjects with AHP must not only understand their current medical state and the available treatment options, but they must also understand why they are being recruited for a research trial in the acute setting, that experimental interventions do not provide a reasonable expectation of success, and how research procedures like randomization and the use of placebo will affect them (Ciccone & Bonito, 2001).

Similarly, the risk of harm and burden as a result of research participation might necessitate a higher threshold of decisional capacity according to the risk-relative standard of decisional capacity (Buchanan & Brock, 1990). The risk-relative standard is determined by the risk:benefit

analysis. Because clinical research might expose subjects to experimental interventions and, in some cases, involve forgoing standard care, the risk:benefit ratio might be substantially less favorable than is typical in clinical treatment scenarios. Moreover, research subjects are exposed to the risk of harm or burden of participation for the primary goal of benefitting others. Direct benefits to research subjects might be substantially less than the benefits received by patients through clinical treatment. Therefore, both the task-relative and risk-relative standard indicate that a higher threshold for decisional capacity is often appropriate in the research context. Decisional capacity and the standard according to which it is assessed is specific to a particular decision. Much as for clinical treatment, prospective subjects might have sufficient capacities to consent to one research trial but not another (Deshpande et al., 2020).

4.2.1 Informed Consent for Subjects with AHP

Patients with AHP may be entitled to additional protections when enrolled in research because they are medically, cognitively, and situationally vulnerable. Prospective subjects who are vulnerable are at a "greater risk of being used in ethically inappropriate ways in research" (NBAC,2001, p. 85) and therefore should be protected from this increased risk of harm (Gordon, 2020).

Because current standard of care treatments for stroke and hemiplegia are limited in their effectiveness, prospective subjects with AHP may be medically vulnerable. The type of stroke, the time since symptom onset, and other patient characteristics dictate patient access to existing treatments. As a result, many stroke patients may not satisfy the clinical criteria to access standard treatments. Therefore, for some patients with AHP, enrolling in research trials that provide the potential for therapeutic benefit may be their only hope to receive potentially effective treatment

for their stroke or hemiplegia. This hope may drive these prospective subjects to enroll in more risky research without adequately understanding the difference between experimental interventions and treatment opportunities. Furthermore, no standard therapy currently exists for the treatment of anosognosia. Patients with AHP might be asked to enroll in early, experimental research trials that aim to treat anosognosia, but such early trials may have low probability of benefitting them.

Moreover, medically vulnerable patients may be especially likely to confuse therapeutic research with therapeutic treatment, i.e., to suffer from "therapeutic misconception" because they lack good therapeutic options within standard of care (Kipnis, 2001). "Therapeutic misconception exists when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial" (Henderson et al., 2007). Subjects suffering from therapeutic misconception fail to understand the protocolized nature of research (and thus fail to recognize that they sacrifice the right of personal or individualized care).

Medical vulnerabilities may bring about or occur alongside cognitive vulnerabilities. Cognitive vulnerabilities are those that impair prospective subjects' capacity to deliberate about and decide whether to participate in a research study, making it difficult for these subjects to act in their own interests. Additionally, subjects with cognitive impairments might be more reliant on others for caregiving. Their dependence on others might expose subjects with cognitive impairments to external pressures that further restrict their ability to act in their own interests. As a result, enrolling prospective subjects with cognitive impairments in research raises concerns about the voluntariness of their decision (Deshpande et al., 2020). Immaturity, dementia, and

mental illness are some examples of conditions that bring about a cognitive vulnerability (Kipnis, 2001).

Prospective subjects with AHP may exhibit cognitive deficiencies as a result of both stroke and anosognosia. An impairment in any one cognitive faculty may limit prospective subjects' ability to attend to and understand the information disclosed to them or evaluate the risks and benefits associated with participation in research in both therapeutic and non-therapeutic research. The damage inflicted by stroke can interfere with patients' ability to consider their options and make informed decisions regarding their medical care (Applebaum, 2007). This interference is particularly debilitating in the research setting where, as I have demonstrated, a higher standard for decisional capacity is required to meet the demands of participation in research according to both the task-relative and risk-relative standards. Previous studies have found stroke patients who enroll themselves as subjects in research trials frequently lack a clear understanding of the purpose or principles of the trials in which they participated (Faris et al., 2023). For example, in a Norwegian thrombolytic trial, none of the stroke subjects had a clear understanding of the purpose of the trial, the implications of entering an experimental trial, or the rationale behind random selection (Mangset et al., 2008).

It is reasonable to expect this problem to be worse for prospective subjects with anosognosia following stroke. Individuals with anosognosia exhibit a resistance to addressing their deficit (Vuilleumier, 2004). On the one hand, this resistance need not extend to their symptoms in general. It is typically only patients' hemiplegia related to their stroke about which they lack, or rather resist, awareness. As a result, prospective subjects with AHP may have little difficulty enrolling in therapeutic and non-therapeutic research trials that draw attention to their symptoms unrelated to hemiplegia following stroke, so long as these prospective subjects are not otherwise

restricted by their lack of capacities. Patients with AHP are sometimes able to acknowledge their stroke, that they are being treated in a hospital, and that they are experiencing other symptoms not related to hemiplegia (Ramachandran, 1996; Bisiach et al., 1986). Therefore, it may not be especially problematic for patients with AHP to enroll themselves in research trials trying to understand non-hemiplegic-related symptoms or administering experimental interventions to address non-hemiplegic-related symptoms of which subjects are aware.

On the other hand, research trials that focus on aspects of subjects with AHP' condition about which they are anosognosic present a real concern about the permissibility of enrolling these patients, because their ability to satisfy informed consent requirements is impaired due to specific cognitive deficits related to anosognosia. Because they cannot appreciate their hemiplegia, patients with AHP are unable to make appropriate decisions for themselves concerning whether to enroll in research to understand or treat their anosognosia or hemiplegia because awareness of these conditions are relevant to how prospective subjects weigh the risks and benefits of participation. Additionally, because awareness of one's hemiplegia is relevant to understanding one's stroke and its impact on quality of life, anosognosia also impairs prospective subjects' ability to make decisions regarding participation in stroke research. Therefore, prospective subjects with AHP are limited in their ability to understand the information disclosed to them or weigh the risks and benefits of research participation in research to understand and treat stroke, hemiplegia, and/or anosognosia.

Prospective subjects with AHP also exhibit certain situational vulnerabilities. Gordon (2020) argues that vulnerability is not an all-or-nothing state. Instead, it occurs along a spectrum whereby particular situations or features place a person at greater or lesser risk of harm, making them more or less vulnerable. Stroke is a sudden, life-threatening condition for which therapy

needs to be rapidly pursued (Saver, 2006). Following a stroke, once patients with AHP report to the hospital, they are launched into a fast-paced sequence of diagnostic testing and therapeutic interventions (Mayo Clinic, 2023). As a result, patients are afforded very little time to weigh their treatment options and make a decision regarding their medical care. Prospective subjects have the added task of deciding whether to participate in a specific research trial. Therefore, prospective subjects can feel pressured by an even smaller window in which to consider participating in a research trial. This time pressure likely exacerbates the effect of prospective subjects with AHP' reduced capacities, and as a result, can impair their ability to provide informed consent (Thomalla et al., 2017).

4.3 How Subjects with AHP Might Nevertheless Be Enrolled in Research

One response to the increased or multiple vulnerability(ies) of potential research subjects is to exclude them from participation because they are at a higher risk of being harmed or experiencing more severe harm (Emmanuel, Wendler, & Gerdy, 2000; Karlawish et al., 2008). This could mean completely removing the opportunity for patients with AHP to enroll in research trials. While this approach would protect prospective subjects with AHP from risks associated with research, it has several shortcomings. The primary problem is that it would prevent both increased understanding of these conditions and development of effective treatments for these patient populations. Secondly, it would exclude such patients from having access to the potential benefits of therapeutic research on their conditions.

Typically, older stroke patients, patients who have suffered more severe strokes, and patients whose stroke brought about cognitive impairments or reduced consciousness are more

likely to lack the decisional capacity required to provide consent (Thomalla et al., 2017). Restricting research enrollment to capacitated subjects will systematically exclude these specific subgroups of stroke patients and result in research outcomes that are not generalizable to the full stroke population. Without generalizable research, future therapeutic options will be limited in their application (Black, 2010; Thomalla et al., 2017). Therefore, the potential societal benefits that justify doing the research are reduced for studies with such restricted inclusion and exclusion criteria (NBAC, 2001).

Additionally, by excluding populations of subjects from participating in research trials, specific groups of people who most urgently need new therapies are excluded from benefiting from scientific innovation (Orfei et al., 2007; Jongsma et al., 2015). Therefore, if satisfactory safeguards can be established to protect vulnerable subjects like patients with AHP, these patients should not be excluded for two reasons: 1) treating patients with AHP is important and it is important that treatments for stroke and hemiplegia are developed that generalize to patients with AHP, and 2) subjects with AHP might receive direct benefit for their stroke and its sequalae from participating in research studies.

Against taking an exclusionary approach to protecting vulnerable research subjects, Kipnis (2001) argues that "each of these vulnerabilities is conceived, not as a flashing red light ordering researchers to stop, but rather as a cautionary signal, calling for proper safeguards" to protect those with particular vulnerabilities from harm or unfairness (p. G-4). Assuming that prospective subjects with AHP lack the decisional capacity to enroll in specific research studies, but that their enrollment is nevertheless important, how can subjects with AHP be allowed to participate in research?

4.3.1 Waiver of Consent

One approach would be to enroll prospective subjects with AHP through a consent waiver. Under certain conditions, like in research that presents minimal risks similar to those encountered in everyday life, institutional review boards (IRBs) may waive the requirement for informed consent so that certain subjects can be enrolled. Current federal regulations require that four criteria be met to be able to waive informed consent: 1) the research involves no more than minimal risk, 2) the waiver will not adversely affect the rights and welfare of participants, 3) the research could not be practicably performed without the waiver, and 4) whenever appropriate, subjects will be provided with additional information about the study (21 CFR § 50.23; 21 CFR § 50.24; NBAC, 2001). The NBAC (2001) views waiving consent as justifiable in research involving "no interaction between investigators and participants, such as in studies using existing identifiable data (e.g., studies of records) and in studies in which risks generally are not physical." (p. xvii).

However, the types of research that seek to enroll subjects with AHP likely include greater than minimal risk and substantial interaction between investigators and research subjects. Research to treat anosognosia, hemiplegia, or stroke in the acute setting is likely to expose research subjects to greater than minimal risk, with or without the prospect of direct benefit. Research to understand anosognosia, hemiplegia, or stroke in the acute setting might expose research subjects to less risk than research to treat these conditions, but research participation might nevertheless substantially burden subjects with AHP due to the attention toward subjects' condition about which they lack awareness. Similarly, outside of the acute setting, research on anosognosia or hemiplegia might expose prospective subjects with AHP to substantial burdens or risk (though, likely less than those present in research in the acute setting following stroke) with varying degrees of direct benefit (e.g., research that administers rehabilitation). According to the regulations described above,

waiving consent is not appropriate in these types of research that enroll subjects with AHP, because it would expose subjects to greater than minimal risks or burdens. On the other hand, if not overly burdensome, research to understand anosognosia, hemiplegia, or stroke that does not impede standard of care treatment for these conditions might satisfy the conditions for waiving consent, because this research is unlikely to pose more than minimal risks to subjects. Even without receiving an experimental intervention, however, subjects with AHP may experience greater than minimal distress as a result of being questioned about their conditions about which they lack and resist awareness. The distress created by non-therapeutic research may disqualify the use of consent waivers. Therefore, while consent waivers may be relevant to a select few research studies that enroll subjects with AHP, the majority of research, and certainly research from which subjects with AHP stand to directly benefit, cannot be conducted through consent waivers.

On the other hand, in emergency situations where subjects are unable to provide consent as a result of their life-threatening circumstance, "Exception from Informed Consent (EFIC)" regulations allow for the requirement of consent to be waived if additional protections of the rights and welfare of subjects are implemented (Ellis & Lin, 1996; Vaishnav & Chiong, 2018; Sattin, 2022; 21 CFR § 50.24). Emergency EFIC is frequently used in the context of stroke research investigating unproven or unsatisfactory treatments where the therapeutic time window is too narrow for reliable surrogate consent (Feldman, Hey, & Kesselheim, 2018). EFIC may be useful for research studies that expose subjects with AHP to experimental interventions to treat anosognosia, hemiplegia, or stroke in the acute setting.

However, the use of EFIC in the acute setting is controversial. In a systematic review of forty-one trials that employed EFIC for testing drugs and devices in emergency settings, most EFIC trials did not demonstrate a benefit from the experimental intervention(s) and were

associated with serious adverse safety outcomes. Additionally, the use of EFIC is associated with racial and ethnic bias in enrollment (Feldman, Hey, & Kesselheim, 2018). Therefore, the application of EFIC in the acute setting following stroke requires further study to determine its ethical acceptability, or it might require procedural modifications to render it acceptable. Finally, EFIC would not be useful for enrolling subjects with AHP outside of the acute setting.

4.3.2 Deferred Consent

With deferral of consent, incapacitated subjects are enrolled into research trials, and at some later point, once they regain capacity, are given the opportunity to continue their enrollment or withdraw from the study (Faris et al., 2023). Although it is not permitted in the U.S., deferral of consent has been used to enroll stroke subjects in a growing number of emergency research trials elsewhere. A large thrombolytic trial in Canada that compares two types of tissue plasminogen activators enrolls its subjects by deferral of consent, thereby allowing for the rapid administration of the thrombolytic drug following stroke symptom onset (Menon et al., 2022). Such deferral of consent may be appealing for trials involving anosognosic subjects, who are likely to regain their awareness at a later point.

In addition to making the enrollment process quicker, deferred consent is thought to increase enrollment and decrease selection biases by not restricting enrollment to capacitated subjects; however, these benefits are not consistent across studies (Faris et al., 2022; Faris et al., 2023). Furthermore, deferral of consent risks enrolling vulnerable subjects who would have refused participation had they had sufficient decisional capacities (Faris et al., 2023).

4.3.3 Advance Consent

Advance consent allows individuals at risk of stroke who would want to participate in stroke-related research to provide consent for research participation should they have a stroke in the future and lose decisional capacity (Faris et al., 2023). Potential patient-subjects at risk for stroke are identified through stroke prevention clinics, where they can receive information about ongoing research trials and provide consent prospectively. Their decisions are documented in their electronic medical record to be enacted at a later time should they lose decisional capacity following stroke (Shamy et al., 2021).

Shamy and colleagues (2021) found that around 5-7% of patients seen in their stroke clinic present to the emergency department with an acute stroke within one year of their clinic appointment. This equals to about 100-150 prospective subjects from one clinic who could be recruited for a stroke trial via advance consent. This number increases to about 1500 patients over the course of one year if advance consent could be obtained at any outpatient clinic. Therefore, a substantial number of prospective subjects with AHP might benefit from providing their advance consent to enroll in a stroke trial.

However, current practice limits advance consent to prospective subjects who demonstrate pre-existing conditions associated with stroke, or who are being treated at a stroke prevention clinic (Shamy et al., 2019; Shamy et al., 2021).[17] Individuals who are not identified as being at risk for stroke are excluded from the opportunity to complete advance consent. Therefore, relying on advance consent will routinely exclude from research participation those stroke patients who have

[17] This practice appears to derive from what is practical, and not necessarily what is ethically permissible.

not experienced a previous stroke and who are not otherwise at risk. Additionally, advance consent to research is subject to the same limitations as advance directives for clinical treatment. The benefit that advance consent provides to potential subjects with AHP is dependent on whether their values and preferences remain constant between the time when they complete an advance consent and when the advance consent is activated (Dresser & Robertson, 1989; Buchanan & Brock, 1990). Moreover, individuals who do not complete a consent for a particular study in advance might nevertheless want to participate in certain types of research (Wicclair, 1993). Furthermore, advance consents for a specific research trial are only applicable to that research trial. On the other hand, if the scope of the advance consent were broad, prospective subjects may unwittingly give consent to research in which they did not intend to participate; broad advance consent does not guarantee contemporaneous consent to a specific research trial (Friedrich et al, 2018; Buchanan & Brock, 1990).

4.4 Surrogate Decision-Making

While these alternatives to informed consent for prospective subjects who lack decision-making capacity could be advantageous to achieve the goals of clinical research and to protect vulnerable research subjects in some cases, these alternatives should only be considered if consent cannot otherwise be obtained from prospective subjects' proxies (Deshpande et al., 2020; 45 CFR § 46.116). Surrogate decision-makers should determine whether to enroll a prospective subject in a research trial according to the substituted judgment principle (Emmanuel, Wendler, & Gerdy, 2000; Vaishnav & Chiong, 2018), guided by evidence of prospective subjects' values and preferences (Wendler & Prasad, 2001). Berg (1996) argues that for prospective subjects who are

unable to provide their consent, surrogate consent is only valid if based on strong evidence of what the prospective subject would have wanted if they were capacitated. Anything less "merely reduces the subject to a thing to be acted on" (p. 28).

However, proxies may have greater difficulty extrapolating from prospective subjects' known values and preferences to make decisions about clinical research than to make decisions about medical treatment (Sattin, 2022). Individuals may more frequently discuss with their proxies their values and preferences about clinical treatment or their broad views about science or altruism, than their views related to specific research. Additionally, the risks, burdens, potential benefits, and procedures of research protocols are often specific to the field in which the research is being conducted, the specific questions it seeks to investigate, and study methods. Even if they specifically wanted to, it may be difficult for individuals to discuss with their proxies their preferences regarding all the various types of research, and even more difficult for proxies to apply prospective subjects' general views to specific research trials. Therefore, surrogates' decisions to enroll incapacitated subjects in research are unlikely to be based on strong evidence of subjects' values and preferences.

As a result, surrogates' decisions might differ from what subjects would decide for themselves if they had capacity. When proxies decide differently from subjects, evidence suggests that proxies tend to err on the side of protecting prospective subjects' welfare—proxies refuse participation in research trials with a higher risk potential (Muncie et al., 1997). While perhaps protective of interests that would generally be ascribed to vulnerable subjects, this approach would fail to respect prospective subjects' self-determination and protect their interests if those subjects' preferences favor enrolling them in a research study.

Due to the difficulty with which the substituted judgment standard is applied to decisions to enroll in research, surrogates tend to use other decision-making standards. Black, Wechsler, & Fogarty (2013) found that only 9% of proxies for individuals with dementia chose substituted judgment as their preferred criterion of decision-making for research. Similarly, Karlawish and colleagues (2008) found that only 24% of proxies based their decision on "what the patient would want" when considering participation in an actual dementia research trial. Instead, the majority of proxies made their decision according to the best interest principle instead of the substituted judgment (Karlawish et al., 2008). The best interest principle instructs proxies to consider what is assumed to maximize prospective subjects' well-being. However, enrollment in research cannot be justified purely by appealing to prospective subjects' objectively ascribed best interests, because participation exposes subjects to the risk of harm in the interest of generating knowledge with only limited prospect of direct benefit in some cases (Vaishnav & Chiong, 2018; Sattin, 2022; Warnock, 1998). For these reasons, an alternate framework for surrogate decision-making for research enrollment would be ethically desirable.

4.4.1 A Framework for Surrogate Decision-Making

In clinical treatment, surrogate decision-making allows a surrogate to provide consent on a patient's behalf to an intervention that is either in the patient's best interest or in keeping with the patient's values and preferences. However, in the research context, surrogate decision-making allows a surrogate to provide consent on behalf of a subject to do something primarily for the benefit of third parties if doing so is either what is also in the patient's best interest or what the patient would have chosen to do if capacitated. Because the decision to participate in research brings with it the potential for harm in a context that has the primary goal of benefiting someone

else, it is unclear whether surrogate decision-makers should be permitted to make research decisions on behalf of someone else in the same way surrogates are permitted to make decisions regarding medical treatment. Therefore, it is an ethical challenge to determine the limits on research risks that surrogates can accept on behalf of incapacitated subjects (Emmanuel, Wendler, & Gerdy, 2000; Karlawish, 2003; Van Rookhuijzen et al., 2014). On the one hand, potential subjects with AHP who lack decisional capacity need to be protected from experiencing undue harm, and especially from experiencing this harm only for the benefits of others. On the other hand, these potential subjects should not be excluded from the possibility of benefiting from participating in research, i.e., either receiving direct benefit, or indirect benefit because of the subject's own values and preferences. Moreover, the quality of research stands to benefit from enrolling a representative sample, and especially from representing those who are most in need of scientific innovation.

Several factors influence the permissibility of surrogate decision-making in research: the level of risk or burden of participation, the level of potential benefit, the social value of the knowledge to be acquired, subjects' assent, and the values or preferences of prospective subjects. In what follows, I will explore how these factors are weighed against each other according to existing standards and apply those standards to prospective subjects with AHP.

4.4.1.1 Risk of Harm or Burden

The risk of harm is used by institutional review boards (IRBs) as a sorting mechanism to determine the level of review required by IRBs (NBAC, 2001). IRBs are groups that are formally constituted and assigned to review and monitor biomedical research involving human subjects. The role of IRBs is to make sure that research studies take the appropriate steps to protect the rights and welfare of human subjects participating in research (U.S. FDA, 2019). Prospective

subjects who lack decisional capacity are at a greater risk of being wronged or incurring additional harm, and as a result, should be protected from the increased risk of harm (NBAC, 2001). Therefore, a lower threshold for acceptable risk is appropriate in studies in which surrogate consent is used to enroll subjects as opposed to studies in which the subjects can provide their own consent(SIIIDR, 2009). Many IRBs support this standard and restrict the permissibility of surrogate consent for incapacitated subjects to research that poses no more than minimal risk, whether or not research offers the prospect of direct benefit to its subjects (Doyal et al., 1998; Kopelman, 2004; Gong et al., 2010).

4.4.1.2 Prospect of Benefit

However, it is arguable that the prospect of direct benefit alters the threshold of acceptable risk for enrolling incapacitated subjects in research via their surrogates. A greater than minimal risk of harm might be counterbalanced by the prospect of direct benefit (WMO 2009; SIIIDR, 2009; Deshpande et al., 2020).[18] As previously discussed, participation in research can benefit subjects both directly and indirectly. Research subjects with AHP might benefit directly as a result of receiving an experimental intervention. Considering the permissibility of surrogate consent only according to a research study's level of potential risk would exclude subjects with AHP from a

[18] In fact, if the prospect of therapeutic benefit is large enough and the risk of harm is minimal then the decision to enroll in research is more similar to decisions to authorize clinical treatment (Belmont Report, 1979; High et al., 1994). Wicclair (1993) argues that when a research trial provides subjects with a treatment that would not otherwise be available outside of the research setting, participation in this research can be argued to be in subjects' best interest. However, clinical research is generally not low in risks and high in expected benefits, and this is the case for research in the acute stroke setting.

large portion of possible research trials aimed at treating symptoms of stroke, including anosognosia, thereby preventing patients with AHP from possibly benefitting from experimental interventions. Even though receiving the experimental intervention might be accompanied by a greater than minimal risk of harm, these risks should be considered in light of the potential direct benefits to subjects. For example, in a therapeutic research trial that exposes subjects with AHP to an experimental intervention aimed at reducing the risk of death in the acute stroke setting, the potential benefit of avoiding death might allow for them to be enrolled via their surrogates even though the risk of harm is more than minimal. Some commentators claim that in research that involves a greater than minimal risk of harm, there must be a prospect of direct benefit to participating research subjects, and the risks should be reasonable in relation to the prospect of direct benefit to subjects (Berg, 1996; Deshpande et al., 2020).

However, taking into account only the prospect of direct benefit to research subjects overlooks the value of indirect benefits that may be just as important, if not more important, to research subjects. Van Rookhuijzen and colleagues (2014) investigated the decision-making process involving elderly research subjects with mild cognitive impairment. The investigators found that the potential for direct benefit was not the main reason the majority of subjects wanted to participate in a clinical research trial, even though the trial did risk increasing heart problems, myocardial infarct, or stroke. For most subjects, altruism was instead their primary motivator for participating. Therefore, subjects with AHP stand to benefit from research in important ways by having their values fulfilled. If particular indirect benefits are equally or more important to research subjects than the prospect of direct benefit, it seems reasonable to allow individual research

subjects to consider those indirect benefits as part of their risk:benefit analysis.[19] But how would a surrogate know that they are of such importance to a person with AHP who lacks decisional capacity?

While some of these indirect benefits are important to research subjects, it would not be ethically appropriate to allow indirect benefits to balance potential risks and burdens of research participation when evaluating the acceptability of a proposed research protocol. First, in the above study, subjects' responses pertained to a clinical research trial with the prospect of direct benefit. Therefore, while fulfilling one's altruistic values provides an important indirect benefit to subjects, it does so in this study when the prospect of direct benefit is also present. As a result, we have reason to be cautious of its results. Second, Emmanuel, Wendler and Grady (2000) argue that indirect benefits should not counterbalance the potential for risk because "otherwise simply increasing payment or adding unrelated service could make the benefits outweigh even the riskiest research" (p. 2705). Although the indirect benefits are important to research subjects and should be acknowledged,[20] it would not be appropriate to allow the prospect of indirect benefits to raise the threshold of risk to which surrogates can expose patients with AHP who are incapacitated. Doing so would inappropriately skew IRB judgments concerning risks and potential benefits such

[19] As Emanuel et al. (2000) point out, there are two risk:benefit analyses involved in evaluating the ethics of clinical research. The IRB evaluates the protocol's risk:benefit ratio. This analysis does not and should not consider indirect benefit, as, in principle, these could be augmented to justify (counterbalance) presenting almost any level of risk to research subjects. Individual research subjects, however, should be permitted to consider the indirect benefits of research participation, such as the ability to benefit others (altruism), as a reason to participate and as counterbalancing the risks and burdens the study presents to them.

[20] Which I will acknowledge as part of subjects' values and preferences in a later section.

that any potential risk could be offset by things like large sums of money for participating in research (NBAC, 2001). Therefore, some limits are needed to restrict the magnitude and scope of harms that can be outweighed by the benefits.

4.4.1.3 Social Value

The value of clinical research lies in its aim to prevent, treat, or cure illness and disease or to generate the knowledge to develop methods to do so (Wendler & Rid, 2017; Emmanuel, Wendler, & Gerdy, 2000). Because stroke, hemiplegia, and anosognosia are serious medical concerns that affect many individuals every year, research that aims to understand and better treat each condition can generate valuable knowledge that has the potential to help those people. the value of this knowledge, together with the prospect of direct benefit to research participants, should be balanced against the potential harms and burdens of research participation (NBAC, 2001). In research that exposes incapacitated subjects to no or minimal risk without the potential of direct benefit, the value of knowledge to be gained could be used to justify surrogate consent (WMO, 2009). In research that exposes subjects with AHP to greater than minimal risk, with the prospect of direct benefit, the risks and burdens of participation are to be balanced by the potential of direct benefit as well as benefits to society. The ethical concern is how to conduct such research while avoiding having incapacitated subjects with AHP used in such studies primarily for the benefit of others (i.e., for social benefit)—having people used in a study for the primary benefit of others, at greater than minimal risk to themselves, without their explicit consent. Only if the potential direct benefit is substantial—both probable and of substantial magnitude—would it seem appropriate for such subjects with AHP to be enrolled by their surrogates.

In research that exposes subjects with AHP to greater than minimal risk, without the potential of direct benefit, it is not clear how the value of knowledge to be gained should be

weighed against the potential risks to research subjects. Without the prospect of direct benefit, vulnerable, incapacitated research subjects are exposed to undue risk for the sake of knowledge that will benefit patient groups or society. Balancing the degree of risk against the value of knowledge to be gained by research might expose subjects with AHP to riskier research purely for the benefit of others. This would use patients with AHP primarily, if not solely, as a means to the ends (benefit) of others. As a result, the value of knowledge to be gained should only raise the risk threshold when accompanied by the potential for direct benefit to those incapacitated individuals to be enrolled. Otherwise, without the prospect of direct benefit, incapacitated subjects should only be allowed to be enrolled via their surrogates in research that has no more than minimal risk (SIIIDR, 2009).

4.4.1.4 Assent and Dissent

Usual well-justified research ethics requirements regarding subjects' assent and dissent present particular problems for enrolling patients with AHP in research. Even when surrogate consent is obtained, typically prospective subjects who are incapacitated should be asked whether they would like to participate (Berg, 1996). Assent, which can be either a verbal or non-verbal cooperation with research activities, is the "affirmative agreement to participate in research" (Black et al., 2010). For those who cannot give consent, their assent is required prior to subject enrollment, and should be re-assessed continually throughout research participation (Applebaum, 2010).

Black and colleagues (2010) describe assent as requiring "a meaningful choice and at least a minimal level of understanding." Requiring assent to participate in research respects prospective subjects' nascent or remaining autonomy, because it allows individuals with limited capacity to participate in the decision-making process to the extent they are able (Black et al., 2010). It

acknowledges that capacity is not an all-or-nothing property; this recognition is particularly important for stroke subjects who may still have residual capacities through which they can hold and express their opinions. Additionally, anosognosia does not entail an overall cognitive impairment, nor does it indicate a complete loss of decisional capacity (Turnbull, Solms & Fotopoulou, 2014). Prospective subjects with AHP can be conscious of their surroundings and some may even be aware that they have had a stroke. They may be able to understand basic research procedures and weigh some of the risks, burdens, and benefits of participation. Arguably, assent may be a way for subjects with AHP to demonstrate that participation is in line with their preferences, at least their current preferences, thereby potentially justifying exposing them to more than minimal risk in light of the prospect of direct benefit (Deshpande et al., 2020).

Dissent is the expression of "an objection to participate in research" (Black et al., 2010). If at any time subjects object to enrolling in the research study, or once enrolled object to continuing their participation, their objection should be respected (Deshpande et al., 2020; University of Pittsburgh HRPO, 2021). While verbal objections are clearly indicative of dissent, dissent can be communicated by more subtle behaviors like expressions of frustration, discomfort, or unhappiness, or passivity (Overton et al., 2012). The American College of Physicians (1989) argues that subjects should be withdrawn by their surrogates if continued participation causes subjects "substantial distress." Black and colleagues (2010) support this recommendation, arguing that "if the individual expresses or indicates an unequivocal or sustained dissent, the patient's wishes prevail over the proxy's consent." Respecting subjects' dissent, thereby avoiding their further distress, protects subjects from unwanted activities and unjustified harm (Black et al., 2010). Enrolling subjects who dissent, against their wishes, in a research trial is damaging to both subjects' trust and broader society's trust in their physicians and scientific research (Doyal et al.,

1998). Additionally, imposing research participation on a subject who does not wish to participate violates their dignity (Black et al., 2010).

Obtaining assent and respecting dissent is typically required for all research involving subjects who are incapacitated, whether or not the prospect of direct benefit is present. In a study of ninety-eight IRBs that accept surrogate consent for research, 62% ask for assent or dissent from their subjects (Gong et al., 2010). It is especially pertinent to research involving greater than minimal risk, with and without the prospect of direct benefit.

However, for prospective subjects with AHP, these recommendations concerning assent and dissent are more complicated. As discussed in section two, AHP increases the likelihood that patients will refuse treatment. They may refuse broad treatments for stroke in the acute setting that indirectly attempt to improve hemiplegia, as well as long-term rehabilitative programs that require awareness of hemiplegia. While the same might not be true in the context of research participation, it is reasonable to think that AHP will increase the likelihood that prospective subjects will refuse to participate in research that similarly draws attention to their stroke, hemiplegia, or anosognosia. This may include research to understand or treat anosognosia with or without the prospect of direct benefit, or research to understand or treat stroke or hemiplegia involving AHP, again with or without the prospect of direct benefit. Therefore, while the prospect of direct benefit to subjects might increase the level of risk to which it would be permissible to expose anosognosic subjects in research via their surrogates' permission, the prospect of benefit may have little or no relevance for anosognosic subjects who are likely to dissent anyway. If dissent is always to be respected, then prospective subjects with anosognosia are likely to be excluded from any research that draws attention to their stroke, hemiplegia, and/or anosognosia. Following this standard might be ethically inappropriate.

Assent and dissent of prospective subjects with AHP are unlikely to reflect their actual preferences, which raises the question of whether their assent and dissent—particularly their dissent—is to be respected. The preferences they express are likely to reflect their false, anosognosia-based beliefs. Adhering to usual research ethics requirements requiring that assent and dissent be respected would prevent patients with AHP from having their true preferences respected (if research participation were their true preference), prevent them from potentially benefitting from research participation, and prevent potentially valuable research on anosognosia, as well as the generalizability of research findings on hemiplegia and stroke to patients with AHP. Arguably, the dissent of those with AHP should not be respected when their enrollment is otherwise justified as described above.

Notably, prospective subjects with AHP who refuse to participate in a research trial as a result of anosognosia will only dissent for as long as they experience anosognosia. AHP commonly occurs in the acute and post-acute phases following stroke (Jenkinson, Preston, & Ellis, 2011), and is known to resolve over time (Cocchini, Beschin & Della Sala, 2002). Therefore, the dissent exhibited by prospective subjects with AHP is typically only temporary. Temporary dissent by incapacitated subjects may be justifiably overridden in the research context in particular circumstances.

In research investigating Alzheimer's disease, for example, proxies justified overriding dissent by citing the amnestic nature of the subjects' condition (Overton et al., 2012). While Alzheimer's disease is a progressive condition and not a temporary one, cognition is known to fluctuate in this disorder. Sleep quality, mood, and even time of year affect the extent to which someone with Alzheimer's disease is incapacitated (Lim et al., 2018). However, relevant here is not how the disorder fluctuates, but that the amnestic nature of Alzheimer's disease creates in

patients the perception of a temporary condition. Because the harm or burden experienced by subjects with Alzheimer's disease is only temporary, surrogates feel that it is permissible to enroll incapacitated individuals if other factors are taken into consideration. However, anosognosic subjects differ from subjects with Alzheimer's disease in that anosognosic subjects might remember dissenting to participation in a research study and having that dissent overridden, while subjects with Alzheimer's disease might permanently forget the event altogether. As a result, the temporary nature of AHP does not result in a temporary harm or burden, and citing its temporary nature is not an appropriate reason to override the dissent of subjects with AHP in research.

Of course, not all anosognosic subjects who dissent do so as a result of their anosognosia. Even without anosognosia, some subjects may object to research participation in principle (i.e., as a reflection of their values and preferences), or to a particular component of research and its risk of harm or burden. As a result, if subjects with AHP refuse to participate in research, efforts should be made to first understand their reason for dissent before discounting such dissent as evidence of true preferences. Therefore, what would be most helpful for surrogates is knowledge of prospective subjects' true values and preferences (Viashnav & Chiong, 2018).

4.4.1.5 Subjects' Values and Preferences

When prospective subjects' dissent or expression of discomfort is due to their temporary conditions, such subjects often have their dissent overridden if enrollment promotes their stable values (Overton et al., 2012). Prospective subjects may have views that are specific to research procedures (e.g., disliking needles or not liking answering questions) or preferences regarding which research studies they want to participate in given the type of intervention, the aims of the research, how risks are balanced against the prospect of benefit, and so on (Deshpande et al., 2020). Prospective subjects might also value more general features of research and its purpose. Altruism,

as previously mentioned, is a common reason subjects participate in research (Black et al., 2010; Van Rookhuijzen et al., 2014). Research participation can be a valuable way for individuals with altruistic interests to make a social contribution, which, in turn, contributes toward their feelings of well-being by having their altruistic interests fulfilled (Warner, Roberts, and Nguyen, 2003).

Even though subjects with AHP may not embrace their long-standing values and preferences regarding research participation in their current anosognosic state, their interests nevertheless survive temporary decisional incapacity. A prospective subject with AHP who believes strongly in research participation, for example, is benefitted by having those interests promoted, even if participation brings with it significant risks (along with the prospect of direct benefit, of course) and even if participation will temporarily bring about distress for as long as they are anosognosic. The temporary distress is mitigated by the long-term benefit of having their interests promoted. As the seriousness of potential harm or distress increases, it is important to make certain that research participation does in fact promote prospective subjects' long-standing view of their interests. Wicclair (1993) argues that "as the seriousness of the possible harm or discomfort to the cognitively impaired person increases, the strength of the evidence supporting the conclusion that the person would have consented should increase." This approach strikes an appropriate balance between respecting the values and interests of cognitively impaired subjects and protecting such vulnerable subjects from undue harm.

However, surrogates often do not know enough about prospective subjects' preferences to be able to enroll subjects in riskier research. This lack of knowledge presents a barrier to enrolling prospective subjects with AHP in a large proportion of research, including research with therapeutic components aimed at treating stroke and its outcomes that may also present greater than minimal risk.

This barrier can be reduced by engaging prospective subjects with AHP in the decision-making process and by obtaining information about their views in a way similar to that recommended in section two for the clinical care decision-making context. The hypothetical scenario would provide the prospective subject with the relevant information regarding their hypothetical stroke and its relevance for study in a specific research trial. Prospective subjects could be asked whether they would enroll in the trial given what participation in the research trial would involve. If the prospective subject says that they would not want to enroll in the research trial, they should be prompted to explain how they reached such a decision. If, however, the prospective subject expresses that they would want to participate in the research trial, they could be prompted further to consider whether they would still want to participate if in the hypothetical scenario they were to object to participation owing to their temporary medical condition, anosognosia. Again, while subjects with AHP lack the capacity to give consent to research, they can nevertheless retain knowledge of their values and preferences and can communicate these with their surrogates. The goal of this exercise is to ascertain these enduring values and preferences.

By involving prospective subjects with AHP in surrogate decision-making, surrogates may gain knowledge of prospective subjects with AHP' long-standing interests. As a result, the strength of the evidential base for surrogates' use of substituted judgment is increased, and surrogates are able to enroll subjects with AHP in research with a greater than minimal risk by justifiably overriding subjects' current anosognosic-based dissent. A decision to enroll in research, if supported by the hypothetical scenario, protects subjects with AHP from undue harm and helps to ensure that the interests of incapacitated subjects are promoted. Arguably, subjects with AHP may even be justifiably enrolled in riskier research without the prospect of direct benefit when such participation will reliably fulfill prospective subjects' values and preferences.

4.5 Limitations

4.5.1 Efficiency of Consent

While the use of a hypothetical scenario may reliably discover prospective the views of subjects with AHP regarding research participation, there is a significant obstacle to its application: the lack of time in which prospective subjects with AHP and their surrogates can engage in the decision-making process in the acute setting. Stroke patients often present to the hospital a few hours following the onset of stroke. Once at the hospital, stroke patients must be assessed and identified as potential research subjects. Surrogate decision-makers need to be located and informed of the research study. This process may surpass the time window in which an experimental intervention to treat stroke (like thrombolytic therapy) can be administered, and as a result prospective subjects with AHP who are incapacitated and require the use of surrogates may not be allowed to participate. Because the hypothetical approach likely lengthens this process, there might be limited research opportunities that can allow surrogates to provide consent for patients with AHP when the research is restricted by time in the emergency setting. As a result, the hypothetical approach might not achieve what it is designed to achieve (at least in the context of research in the acute setting)—namely, allowing more patients with AHP to participate in research studies when such participation accords with subjects' values and preferences.

In situations where the values and preferences of patients with AHP cannot be determined reliably within an appropriate time window, the current standards described above according to which surrogate consent is permissible for incapacitated research subjects should apply—namely, surrogates may be able to provide consent for subjects with AHP if the research study presents no more than minimal risk, or if it does present more than minimal risk, presents subjects with the

potential for direct benefit proportional to the risks. Arguably, in research that is so time-sensitive, surrogates may not be located in time at all. As a result, EFIC standards or restrictive approaches will apply.

4.5.2 Dissent and the Distress It Causes

If the research is not otherwise constrained by time pressures, then the hypothetical exercise may assist surrogates in their reconstruction of the true values and preferences regarding research participation of patients with AHP. However, subjects with AHP are unlikely to experience enrollment in research in accordance with their true values as a benefit as long as they are anosognosic. Because their responses to the hypothetical scenario will be used to guide a real action which results in their being enrolled in the research trial, they may actively dissent from such participation. Because people generally enjoy and thus have an interest in making decisions for themselves, subjects with AHP may be psychologically harmed by their surrogates' decision even if these decisions promote the value of self-determination. While I have argued that this harm, which is likely temporary, is mitigated by the long-term benefit of having one's interests promoted and true values respected, prospective subjects with AHP may still be distressed. Their immediate, even temporary, distress is an aspect of enrolling them with which subjects, their surrogates, and all research personnel must contend.

Strong evidence of prospective subjects' values and preferences allows for surrogates to enroll subjects with AHP in riskier research, even without the prospect of direct benefit if research participation is likely to benefit subjects through value fulfillment. The result is increased participation in research, which is reasonably anticipated to benefit the quality of knowledge produced without jeopardizing the rights and welfare of incapacitated subjects with AHP.

However, these benefits are unlikely to extend to research conducted under extreme time pressures in the emergency setting. Additionally, the benefit to subjects with AHP might not be perceived by these subjects due to the nature of anosognosia. Therefore, while the use of a hypothetical scenario is generally advantageous, it does not completely solve the complications associated with surrogate decision-making for research subjects with AHP, and further effort should be devoted to ameliorating subjects with AHP' potential distress.

5.0 Conclusion

AHP is a heterogenous condition in which patients lack awareness of their hemiplegia; sometimes this lack of awareness extends to their stroke and its range of symptoms. Sometimes, however, patients with AHP lack only the explicit awareness of their hemiplegia. Explicit awareness is necessary for patients with AHP to authorize or refuse treatment for their hemiplegia or stroke, because of the relevance of paralysis for their judgment of their quality of life and use of this evaluation in weighing their treatment options. Acute treatments for stroke or hemiplegia aim to prevent death and reduce the likelihood and impact of long-term disability, but pose significant risks to patients. Therefore, a decision to authorize acute treatment for stroke or hemiplegia must be weighed against patients' values and preferences, including their view of their quality of life. Because patients with AHP might lack decisional capacity to make acute treatment decisions regarding their hemiplegia or stroke, their surrogate decision-makers must instead make acute treatment decisions on behalf of patients with AHP, taking into account patients' values and preferences.

Patients with AHP, however, should not be completely excluded from decision-making regarding their medical condition, because decisions to authorize or refuse acute treatments for hemiplegia or stroke involve normative judgments and have serious consequences. Even without awareness of their hemiplegia, patients with AHP retain specialized knowledge of their values and preferences. This paper argued that the values and preferences of patients with AHP may be elicited by their surrogates through the use of a hypothetical scenario and abstract questioning. By involving patients with AHP in their hemiplegic state in surrogate decision-making, the strength of surrogates' evidential base for decision-making may be increased. As a result, surrogates may

be assisted in reconstructing Patients with AHP' values and preferences, and the decision to authorize or refuse acute treatment for stroke or hemiplegia may more reliably reflect what patients with AHP would decide if they had capacity.

The same technique can be used for decisions to enroll patients with AHP in research. This approach is particularly important in the research context because unlike clinical treatment, research is conducted toward a goal of producing generalizable knowledge, not benefitting individual research subjects. As a result, it is difficult to justify enrolling incapacitated individuals in research through their surrogates due to the risk of harm and burdens of research participation without the reasonable expectation of direct benefit, if indeed it is permissible at all. Reliably knowing prospective subjects' values and preferences would allow surrogates to enroll these subjects in riskier research when doing so would promote prospective subjects' own view of their interests.

5.1 Avenues for Empirical Testing

While the approach proposed in this project respects the right of self-determination of patients and subjects with AHP, as long as they are anosognosic, they might nevertheless perceive their right of self-determination as being violated and actively dissent from participation in treatment or research; as a result, they might experience substantial distress. This is problematic for three reasons. First, acting in a way to which individuals with AHP actively dissent may lead them to experience feelings of anger, frustration, or distress. The experience of these feelings are contrary to patients their current, and perhaps their enduring, interests. Second, their dissent, or the experience of having their dissent overridden, might debilitate these individuals further by

exacerbating the effects of the neuropathology already present. Third, their dissent and consequent distress might undermine the positive effects of treatment or the validity of research data.

Perhaps, however, individuals with AHP will not experience feelings of dissent or experience having their dissent overridden when the decision is made and applied to them in the moment. These dynamics can be empirically discovered, and further research should be devoted to applying the hypothetical approach to surrogate decision-making involving patients and subjects with AHP, and then monitoring their responses to the exercise as well as to the implementation of the surrogate's decision. Especially in the research context, attention should be paid to how prospective subjects with AHP respond to their surrogates making research decisions and to whether prospective subjects object to allowing their surrogates to decide for them in the first place.

5.2 Applying This Analysis to Other Conditions

Despite this project's focus on AHP, its analysis of surrogate decision-making involving individuals with AHP may provide a foundation for thinking about the process of informed consent for other conditions about which anosognosic individuals lack awareness. One's lack of awareness is specific to the condition about which one is anosognosic. The specificity of unawareness might allow individuals to engage in the decision-making process with their remaining capacities. However, the degree of functional specificity varies according to the condition of which one lacks awareness, as do other features of the unawareness. As a result, the degree to which individuals who lack awareness of their condition can participate in the decision-making process will vary, as will the approach to engage these individuals in that process.

In psychiatric conditions, a lack of awareness of one's condition or of a symptom of one's condition can fluctuate with the psychiatric condition, and the lack of awareness is complicated by other neuropsychological symptoms. It is difficult for these patients to return to a stable state of awareness. Similarly, anosognosia in neurocognitive disorders is not usually temporary and, in fact, worsens with time. Therefore, it is unclear how patients' past values and preferences should be considered in light of their current and future values and preferences, given that their condition might not improve over the course of their life and may even worsen. Additionally, the type of treatment for each condition about which one can be anosognosic will impact the permissibility of surrogate consent. For example, antipsychotic medication, in clinical practice and in research, is associated with severe and persistent adverse effects. Patients with anosognosia experiencing psychosis might not appreciate the benefits of these medications, but they do recognize the adverse effects (Strieff, 2023). These concerns need to be separately considered, but with the understanding that even without decisional capacity patients and prospective subjects with anosognosia might be able to contribute toward decisions about their care and research contribution.

5.3 Further Directions for Additional Ethical Analysis

In addition, this project suggests the need for continued ethical analysis of the validity of advance directives. I have demonstrated how implicit knowledge of one's hemiplegia following stroke can be used to inform one's values and preferences. Individuals' more informed, contemporaneous preferences should inform the decision-making of their surrogates and should be given greater weight than those preferences expressed in their advance directive, because informed preferences are likely to result in a decision that reliably reflects patients' and subjects'

view of their interests. Accepting this argument, however, would undermine not only the validity of these individuals' advance directives, but also the whole concept of an advance directive, which is to have past preferences expressed while one has decision-making capacity be used by one's surrogate to make decisions when one lacks such capacity. Therefore, along with the arguments by Dresser and Robertson (1989), the argument of this project warrants continued ethical analysis.

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