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Title: A Systematic Literature Review of Animal Assisted Interventions in Oncology (Part II): Theoretical Mechanisms and Frameworks

Authors: Holder TRN[1]*, Gruen ME[2], Roberts DL[3], Somers T[4], Bozkurt A[5]

Affiliations: [1]University of North Carolina and North Carolina State University Joint Department of Biomedical Engineering ; [2]North Carolina State University Department of Behavioral Medicine ; [3]North Carolina State University Department of Computer Science ; [4]Duke University Department of Psychiatry and Behavioral Sciences ; [5]North Carolina State University Department of Electrical and Computer Engineering

*__Corresponding Author__: Timothy R. N. Holder ; Email: trholde2@ncsu.edu

Abstract: Animal-assisted interventions (AAI) are a unique class of complementary medical treatments that can improve a patient's quality of life, both physically and psychologically. Part I of this two-paper systematic literature review series focused on the study methods and quantitative results of researchers in this field. We continue this in-depth review here in Part II by discussing the common theories associated with AAI in the context of cancer. Of all the factors at work in human-animal interactions, researchers explicitly cite compatible animal personality, physical touch, physical movement, distraction/entertainment, and increased human interaction as the mechanisms responsible for the positive clinical outcomes observed in AAI. In various combinations, these mechanisms group under broader theoretical frameworks that attempt to fully explain the AAI context as it relates to cancer care. The social support hypothesis and the conception of a human-animal bond are the most referenced overarching frameworks. The cognitive activation theory of stress, the science of unitary human beings, and the self-object hypothesis are also referenced. We briefly consider other relevant theories commonly noted in the human-animal interactions literature that have the potential to clarify aspects of cancer-related AAI. We also discuss the neurobiological transduction mechanisms needed to connect theoretical frameworks and their mechanisms directly to the observed clinical outcomes. To advance the field, researchers should consider overarching theories with testable hypotheses when designing studies, and use consistent terminology when reporting results. This review lays a foundation for progress towards a unified theoretical framework and for effective treatment of the whole cancer patient.

Keywords: animal-assisted interventions, animal-assisted activities, animal-assisted therapy, oncology, cancer, human-animal bond, mechanisms, theoretical frameworks

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Introduction

A cancer diagnosis presents a threat to a patient's physical, psychological, and social well-being. Often, cancer patients experience deleterious health effects due to the significant stress of managing cancer and its treatments.[1] This stress can lead to significant social isolation by affecting relationships with loved ones and medical staff.[2,3] It also contributes to cancer-related symptoms such as fatigue which may negatively impact mood and potentially immune function.[4,5] Providing a holistic treatment thus requires attending to the psychosocial aspects of cancer as well as the physical disease even though addressing these psychosocial aspects is complicated. For example, overt offers of assistance may hamper effective social support and threaten a patient's self-esteem by forcing him or her to seem "helpless or dependent."[6,7] For pediatric populations, the physical and emotional harm caused by a cancer diagnosis increases a child's "vulnerability to the development of psychological disorders, which may directly or indirectly affect their general clinical condition."[8] Complementary and alternative treatments offer potential solutions to meet these psychosocial needs. These treatments include medical products and practices that are not part of standard medical care, but can still produce observable benefits for patients.[9–11] Since 1961, researchers led by Boris Levinson began to awaken to the idea that certain positive interactions with domesticated animals can provide benefits to humans.[12,13] Animal-assisted interactions (AAI) is a complementary medical treatment drawing on this concept, using sessions with animals to improve clinical outcomes. Researchers use AAI to ameliorate problems their subjects face while also investigating it as a broadly applicable treatment modality. In Part I of this systematic review series, we specifically reviewed the literature on AAI in oncology with a special focus on study designs and quantitative results.[14] Similar to the field limitations we highlighted in that article, several comprehensive and partial reviews have criticized the AAI field "for inadequate methodology, dubious analyses of results, and questionable conclusions."[15–17] While many issues for cancer-related AAI as a field stem from methodological and analytical inconsistencies, a general paucity of rigor in the theoretical underpinnings of these therapeutic interactions is a significant hindrance to understanding what works during an interaction.[18–20] Comparatively, few research studies in cancer-related AAI propose testable hypotheses or are rooted in a theory of what makes AAI effective. This limits the value researchers can extract from their hard work or from results that are sometimes positive, but often neutral. Ignoring theoretical considerations in the field of AAI perpetuates a lack of empirical evidence, slowing progress towards a general understanding of how best to employ this alternative treatment. Lexical inconsistencies further compound these problems when AAI is parsed into its sub-fields. Different definitions have been proffered in good faith and many terms in the field (such as pet therapy or animal facilitated therapy) have been used interchangeably despite calls for a more consistent use of terminology.[19,21] However, it is generally understood that, under the broad umbrella of AAI, animal-assisted activities (AAA) seeks to improve patient quality of life broadly while animal-assisted therapy (AAT) is

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targeted towards generating specific clinical outcomes (e.g. lower blood pressure or reduced cancer-related fatigue.)[18,19,22–24] For the AAI studies lacking a solid theoretical basis, the meaningful distinction between AAA and AAT can often evaporate, becoming purely a matter of linguistic preference. Nevertheless, the research results laid out in Part I of this review series are still valid and useful.[14] In Haylock et al.[25], the authors note that they use the qualitative methods available to determine the beneficial effects of a cancer-related AAI. It follows that, from this quantitative assessment, a theoretical framework can be extrapolated. Thus, there are two research paths: starting with a testable hypothesis or extrapolating explanations after the fact. In either, a "sound theoretical basis supported by scientifically measured physiological parameters is needed to gain medical support for animal-assisted therapy."[26] As Hosey et al.[21] details in their comprehensive review of the human-animal interaction field, frameworks produced via either strategy, and the accompanying research, are not concerned with theories outside of their own context even if certain themes can be seen throughout the field. This said, there are several theories that purport to explain the mechanisms and reasons why the human-animal bond is generally positive and why AAI works in oncology. In this Part II of a two-paper systematic literature review series, we discuss the theoretical frameworks and mechanisms directly invoked by the cancer-related AAI articles included in Part I, paying special attention to the theories authors provide to explain results.

Systematic Review Methods

We conducted a systematic literature review focusing on various terms for both AAI (including animal facilitated interventions, pet therapy or equine assisted activities) and cancer (such as neoplasm or oncology). More details on the literature search methodology are provided in Part I on this systematic review. The full literature search gathered any document format up to July 31st, 2018 by interrogating the PubMed, Web of Science, Scopus, CAB abstracts, CINAHL, Google Scholar, and North Carolina State University, and University of North Carolina-Chapel Hill's library databases. Full and partial readings of the results for specific relevance to our review's topic sentence resulted in 32 relevant publications. In this context, relevance is defined as providing independent, novel data or summary information specifically dealing with the efficacy of AAI and its variants in oncology. The studies' methods and results were summarized in Part I of this two-paper series and the discussed theoretical implications discussed by these 32 articles summarized in this Part II review.[14] A general review of the AAI literature revealed other theories of interest not mentioned by papers included in this review of AAI in oncology and these theories are also discussed. A summary of the discussed theories' postulates and several relevant cancer-related AAI articles are organized in [**Table 1**].

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Table 1 Theoretical concepts in AAI with cancer-related references.

	Concept	Main Tenets	Cancer-related AAI Reference
Mechanisms	Compatible Animal Personality	> humans can respond to the natural attributes of therapy animals. > both patient and animal temperaments affect the success of therapeutic interactions.	Chubak et al.[28]; Haylock et al.[25]; Ginex et al.[29]
	Physical Touch	> physically touching a therapy animal comforts and benefits the patient directly.[43-45]	Kaminski et al.[38]; Cerulli et al.[39]; McCullough et al.[31]; Schmitz et al.[33]; Haylock et al.[25]; White et al.[66]
	Movement	> movement motivated by physically interacting with the therapy animal provides exercise-like benefits.[33–36]	Caprilli and Messeri[37]; Kaminski et al.[38]; Orlandiet al.[11]; Haylock et al [25]: Cerulli et al [39]
	Human Interaction	> therapy animals can both ease and increase the interactions between patients and other humans: a "social catalyst" effect.[2,45,55,107] > increased human interaction directly benefits patients and enhances their general healthcare environment.[11]	Orlandi et al.[11]; Ginex et al.[29]
	Distraction/Entertainment	> the novelty of an entertaining AAI visit benefits patients by distracting them from the gravity of their diagnosis or the side effects of their medical treatment regimen.[8,25]	Kaminski et al.[38]; Haylock et al.[25]; Moreira et al.[27]; Yom[30]; Silva et al.[8]
	Attentionis egens	> denotes the "need for attention on a normal, basic emotional level as the prerequisite for successful social interaction."[26] > the success of AAI comes from bi-directional attention-seeking behaviors (where the therapy animal replaces another human.) > the therapy animal's attention-seeking inspires prosocial behaviors that strengthen the human-animal bond.	–
	Sensory Stimulation	> expands on the physical touch mechanism to cover all human senses (i.e. canines can affect each of the senses to lower cortisol and engender "physical benefits including a decrease in blood pressure, heart rate, and respiratory rate.")[32,96,97]	–
	Responsibility/Task Completion	> successfully completing activities with a therapy animal can boost patient self-esteem and sense of accomplishment.[16,101]	–
Theoretical Frameworks	Biophilia Hypothesis	> humans have a natural attraction to other living things—both flora and fauna.[21,57] > biophilic attraction can open the door to more complex human-animal interactions.[28,58,59]	Chubak et al.[28]; Coakley and Mahoney[58]; Kumasaka et al.[59]
	Social Support Hypothesis	> humans exist in support networks of varying complexity and magnitude that can define how they react to stress.[60-64] > the therapy animal is a special node in the patient's support network as (a) it can not judge the patient and (b) may benefit the patient in ways humans can not.[45]	Marcus et al.[65]; White et al.[66]; Yom[30]; Petranek et al.[66]; Muschel[69]; Silva et al.[8]; Kumasaka et al.[59]; Schmitz etal.[70]; Bibbo[71]
	Human-Animal Bond	> "the dynamic relationship between people and animals such that each influences the psychological and physiological state of the other."[21,72-75] > a positive human-animal relationship may precede the formation of a bond, but the human-animal bond refers to one patient's mutual connection to a specific, non-interchangeable therapy animal.[21,83,84] (*)	Silva et al.[8]; Orlandi et al.[11]; Chuak et al.[28]; Ginex et al.[29]; McCullough et al.[31]; Cerulli et al.[39]; Coakley and Mahoney[58]; Chubak et al.[76]; Johnson et al.[77]; Haylock et al.[25]; McCullough et al.[54]; Fleishman et al.[78]

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Table 1 (cont.) Theoretical concepts in AAI with cancer-related references.

	Concept	Main Tenets	Cancer-related AAI Reference
Theoretical Frameworks (cont.)	Self-Object Hypothesis	> the therapy animal is viewed as an ideal object with which the human forms a stable attachment.[85] > therapy dogs specifically improve a patient's life as they are non-judgmental and display joy when interacting with bonded persons.[70,86–88] > for a patient, positive AAI effects come from a better understanding of the self through interaction and bonding with the therapy animal	Petranek et al.[68]; Johnson et al.[79]; Schmitz et al.[70]
	Cognitive Activation Theory of Stress	> AAI is only useful to a patient in so much as it helps to positively mediate patient responses to the stresses of cancer diagnosis and treatment.[89,90]	Buettner et al.[89]
	Science of Unitary Humans	> organisms are considered as energy fields (consisting of body, mind, emotions, and environment) and psychological variables directly affect stress hormones, immune function and thus well-being.[58,77,91,92] > in AAI, the human's field interacts with the therapy animal's field, reducing physiological stress and increasing positive affect for both parties.	Coakley and Mahoney[58]
	Affection Exchange Theory	> "affectionate expressions often initiate and accelerate relational development" and are thus "key to human survival."[32,102] > the mutual exchange of affection between patient and therapy animal directly results in "enhanced physical and mental well-being experienced by AAI participants."[32]	--
	Attachment Theory	> attachment is properly defined as an "an affectional bond with the added experience of security and comfort obtained from the relationship."[83,84] > the quality of the human-animal bond directly correlates with the psychological and physiological benefits either party derives from the relationship.	--
Transduction Mechanisms	Neurobiological transduction mechanism	> broadly refers to the neurological or biological pathways that cause the observed physiological or psychological outcomes in AAI. > though there is likely some overlap, each AAI mechanism may have its own neurobiological pathway.[26,48,103,105,106]	Moreira et al.[27]; Johnson[79];
	Oxytocinergic System (in AAI)	> the hypothesis (a) that all AAI mechanisms aim to release the affiliative chemical oxytocin, and (b) that the observed AAI benefits come from stimulating the oxytocinergic system.[96,107-111]	--

(*) Though valid, the distinction between human-animal relationships and bonds is often unclear in the language used by AAI researchers.

Proposed Mechanisms of AAI studies in Oncology

Part I of this systematic review series makes the case that AAI in oncology will greatly benefit from specific methodological improvements and further quantitative evaluation.[14] However, more attention to the underlying reasons for the observed effects will also impact this work and better illuminate the path to AAI's

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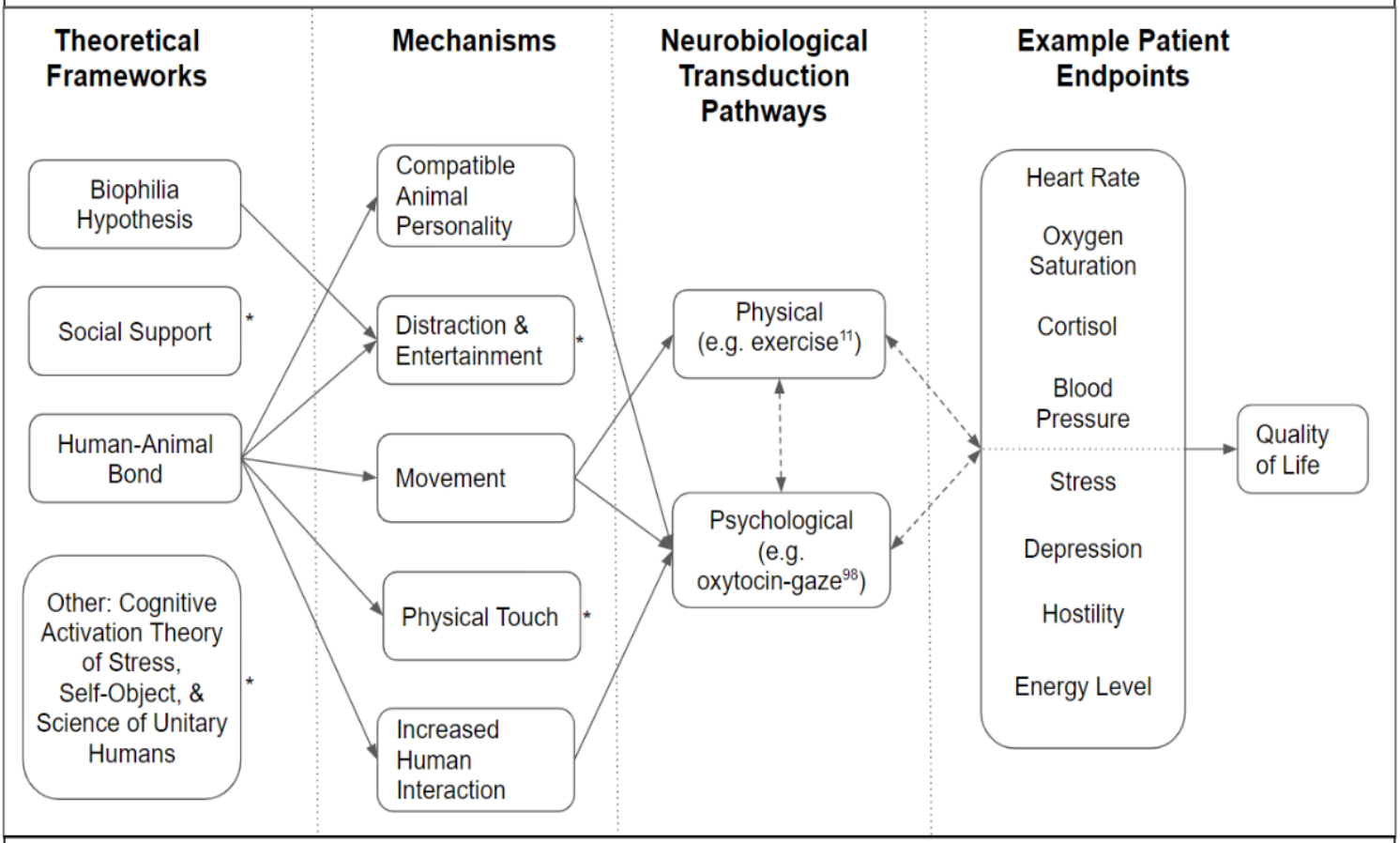
wider acceptance. Several papers included in Part I cite or support existing theories as potential explanations for their results. These individual mechanisms and theories are not mutually exclusive and can be grouped together under a "multi-layered benefit hypothesis."[27] First, it is likely that multiple, overlapping mechanisms best explain how animal-assisted interventions result in the observed effects. We can then group these mechanisms under broader theoretical frameworks in order to define the entire AAI scenario from a high-level perspective and in order to predict certain experimental outcomes. **Figure 1** is an example visual representation—moving from theoretical frameworks to patient endpoints—of how the multi-layered benefit hypothesis could work in cancer-related AAI to improve patient quality of life.

The most commonly cited and supported mechanisms of action are animal personality, novel distraction or entertainment, movement, physical touch, and increased human interaction. Here, we define each mechanism and cite the studies that invoke them to explain results before discussing the implications to AAI in cancer care.

Fig 1. Diagram of multi-layered benefit hypothesis for AAI in oncology.



* Arrows for this concept removed for simplicity.
** Solid, single arrows indicate potential directionality between concepts while dashed, double arrows indicate interplay or feedback loops between concepts.

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Compatible Animal Personality Mechanism

Compatible animal personality is less a standalone mechanism than a beneficial attribute discussed in Part I of this systematic review series with the study designs and animal breeds used. This means that humans can respond to the natural attributes of the therapy animal and that there may actually exist a class or range of temperaments—for both the animal and the human—that are more ideal for AAI activities than others (i.e. a calm vs. aggressive personality.)[51–53] In Chubak et al.[28], 8 of 18 (44%) inpatient youth participants with cancer reported some variation of the dog being calm or relaxing as what they liked most about AAI. Haylock et al.[25] specifically sought out laid-back therapy animals while Ginex et al.[29] recruited energetic characters. While the authors make a point to note these preferences, there is no substantive difference in the results of these papers that can be reasonably attributed to the animal's personality. Regardless, this is certainly an area of interest for improving the prescription of AAI to individual patients with cancer. For example, some patients will benefit from relaxing interactions provided by calm pets while others may prefer the movement and playful touching encouraged by a more energetic therapy animal. Moreover, the mechanism of compatible animal personality bolsters the case for incorporating other non-canine animals into AAI in oncology, not only to alleviate infection concerns and transcend particular animal aversions, but also to increase this complementary treatment's fit to each patient. Some patients may prefer calming interaction with an AAI dog during chemotherapy while others may benefit from active interaction with a trained horse to gain the most benefit.

Distraction and Entertainment Mechanism

The distraction or entertainment mechanism holds that an animal visit can serve to break up the monotony of regular or hospital life for a patient and that many observed benefits come directly from the novelty of AAI in a given moment. Some authors mention novelty-type explanations in passing when explaining results.[25,27,30] Silva et al.[8] goes so far as to state that the distraction effects of canine assisted interactions are notable. As with previous mechanisms, this distracting effect extends to equine assisted therapy with patients regarding the AAI as a diversion from stressors related to a cancer diagnosis and treatment.[25] If accurate as posited, this distraction mechanism may have an interesting corollary: longitudinal AAI studies would see a benefit in the beginning that tapers off with sufficient time after the novelty of pet therapy fades. McCullough et al.[31]—who made every effort to pair individual subjects with the same therapy animal throughout their study—reported no significant changes in any tested parameter for patients before and after the full data collection period (e.g. 4 months per patient). These and similar results in mind, researchers may have to choose between encouraging a bond with a particular animal, as in McCullough et al.[31], and introducing a new therapy animal each session to maximize novelty —the latter potentially an unscalable, resource-intensive proposition. Distraction mechanisms leave space for other complementary and alternative medicines to be

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similar to AAI in usefulness for oncology—provided that they are sufficiently novel and distracting (i.e. as entertaining as a dog rolling over or wagging its tail.)[32] Despite this, Moreira and colleagues—and the authors of this literature review—suggest that there are deeper reasons (e.g. the physical touch mechanism) beyond or in addition to mere distraction that result in the observed benefits of AAI.[27] Additionally, constantly introducing new therapy animals to maintain this effect could be prohibitively taxing on the therapy teams, the patients, and the resources of the AAI program.

Movement Mechanism

The movement mechanism relies on physical exercise explicitly. As opposed to sitting quietly and stroking a therapy animal, this mechanism would provide an impetus for participants to move around with the therapy animals and experience the concomitant benefits of such exercise.[33–36] Support for this mechanism within cancer-related AAI comes from Caprilli and Messeri[37]–who allowed sufficiently ambulatory patients to walk the therapy dog–and Kaminski et al.[38]–who included the dogs in a child-life playroom. Orlandi et al.[11] also emphasized that the significant increase they observed in the AAI group's oxygen saturation may be due to physically moving about and interacting with the therapy dog as opposed to only sitting while receiving chemotherapy. Both Haylock et al.[25] and Cerulli et al.[39] lead studies that include participants' walking and riding horses to positive effect, further supporting the physical movement idea. This physical activity mechanism necessarily excludes many patients who may not be sufficiently ambulatory from experiencing the benefits of AAI that are due to increased movement. The movement mechanism does not account for the vast majority of studies that prohibited vigorous activity but still observed benefits from AAI. Thus it is likely that movement is an advantage to AAI but certainly not the sole—or even arguably the major—source of its benefits, though its prospective benefits similarly cannot be ignored.[40–42]

Physical Touch Mechanism

The physical touch mechanism explicitly refers to the stroking of the animal as the external mechanism for benefits seen in AAI.[43] Stroking a dog's fur provides tactile comfort, decreases tension and allows patients to feel safe in their environment.[44,45] Odendaal[26] goes so far as to say that touching a therapy animal satiates a "skin hunger" or innate desire to be touched in patients and other isolated individuals. Support for these ideas comes from Kaminski and colleagues who contend that affiliative touching contributes more to AAI's effects than cognitive factors, even though the experimental group in their work saw only mood and behavior changes compared to a control group.[46] They cite work by Friedmann et al.[47] that shows contact comfort with a dog was significantly associated with a reduction of heart rate and blood pressure. In their discussion, Cerulli et al.[39] extend the importance of physical touch to equine assisted therapy, noting that the physical contact of grooming

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and riding bolsters a rider's relationship with a horse. In Mccullough et al.[31], the activity most selected by children (92%) and parents (55%) alike was petting the therapy dog; this result is the rule rather than the exception in the studies coding patient-animal interactions. Odendaal and Meintjes[48] observed that physical touch between a human and an animal directly elicits certain biochemical effects such as increases in oxytocin and beta-endorphins. Charnetski et al.[49] and Barker et al.[50]'s work on stroking's ability to increase Immunoglobulin A is potentially relevant to decreasing certain risks of infections and illnesses in oncology. Despite this evidence supporting the benefits of affectionate touching between human and a therapy animal, there remains some doubt in the field. That is, some studies have shown similarly positive effects using stuffed animals—which are comparably pleasant to touch—as compared to live animals,[51] while other work appears to contradict these findings.[52] Additionally, certain forms of touching may be experienced as unpleasant for the therapy animal.[53] However, for several of the studies included in this review, stroking the therapy animal was the most common affiliative behavior, accompanied by very few signs of high stress from the animals involved.[31,38,54] These contrasting results can challenge the idea that a live animal is needed to experience beneficial effects similar to those of AAI. However, physical touch is only one of several mechanisms active during AAI and the combination of several such mechanisms inherent to human-animal interaction may ultimately be what fully makes animal-assisted interventions beneficial.

Increased Human Interaction Mechanism

While seemingly misplaced in the sphere of animal-assisted interventions, increased human interaction as a mechanism speaks to the positive effects that occur when a therapy animal eases the interplay between humans.[2,45] Simply, amiable social interactions with other humans can provide observable benefits to patients and therapy animals can serve both to facilitate these interactions and as a non-contentious topic of discussion.[55,56] Orlandi et al.[11] suggest that even the additional care given by medical staff when distributing questionnaires and monitoring vital parameters during AAI could reduce patient anxiety. This assertion may explain the identical effects observed in both the control and experimental groups of Orlandi and colleagues' study. Regarding AAI in an acute care setting, Ginex et al.[29] similarly posit that AAI-inspired collaboration between various medical services enhanced the healing environment. The essence of the human interaction mechanism would thus be that AAI—in addition to having direct positive effects on patients—also initiates a cascade of positive events or environments that improves patient outcomes. It follows from the formulation of this mechanism that the therapy animal promotes beneficial interactions with the friendly animal handler and with other patients in a group treatment setting. However, quality time and interactions with the therapy animal could be limited in a group setting so increased human interaction and direct benefits offered by the therapy animal must be appropriately balanced in these scenarios.

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Proposed Theoretical Frameworks of AAI studies in Oncology

The overarching frameworks explicitly cited by AAI researchers in oncology include the biophilia hypothesis, the social support theory, the general human-animal bond theory, the cognitive activation theory of stress, self-object hypothesis, and the science of unitary humans. Here, we discuss how the biophilia hypothesis opens the door for both the social support theory and the conceptualization of a human-animal bond before discussing other potential frameworks for understanding AAI's effects.

Biophilia Hypothesis

The main ideas of the biophilia hypothesis were laid out by Stephen R. Kellert and Edward O. Wilson in 1993 and hold that humans have a natural attraction to other living things—both flora and fauna.[21,57] For animal-assisted interventions, this idea provides for the initial impetus of the subject to interact with the animal. Thus, the biophilia hypothesis—specifically channeling the distraction mechanism—could also explain the benefit received from single session animal interventions of short duration where neither full integration into the patient's support network nor the development of a bond has reasonably had time to occur. We also contend that the innate attraction insinuated by Kellert and Wilson's hypothesis can open the door to and undergird any future bonds or networks formed with the therapy animal. Even though the quantitative data are open to interpretation, results from single intervention and short-term studies showing most participants were eager to see the pet enter the room and smiling throughout the intervention lend credence to the idea that biophilic attraction can open the door to more complex human-animal interactions.[28,58,59]

Social Support Hypothesis

The social support conception of AAI is closely related to general social support theory. The latter contends that humans essentially exist in support networks of varying complexity and magnitude that can define how they react to stress.[60–64] For AAI under this framework, the therapy animal is inserted as another useful node in a patient's support network. However, the therapy animal as a special node avoids certain pitfalls, and provides more benefits than traditional human interactions (e.g. the therapy animal cannot judge the therapy recipient.)[45] Marcus et al.[65] specifically note that "kids and families need a support group" when discussing what AAI offers to patients in oncology. Similarly, White et al.[66] provides several anecdotes showing that the therapy animal adds to the counseling support network such as "I was more open to the [counselor] than I have been with other people [counselors] in the past" and "they're just very comforting, I think, dogs are very not judgmental." Other researchers also comment that a therapy animal can be a non-judgemental listener[30,59,67–69] or facilitate interactions with medical staff,[8,66,69–71] both increasing a patient's sense of perceived support during stressful treatment processes. This conception of patient support can also explain previously discussed

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mechanistic vehicles such as compatible personalities, positive physical touch, improved human interactions and the underlying neurobiological factors seeing that therapy animals are specifically introduced to patients as part of the medical support staff. At best, this theory explains the distraction and movement mechanisms indirectly, since both can be, but are not, definitive functions of support groups. It is worth noting that the social support theory often cited by AAI researchers is extremely general by definition and thus lacking in predictive power.

Human-Animal Bond Hypothesis

The Center for the Human Animal Bond defines the human-animal bond as "the dynamic relationship between people and animals such that each influences the psychological and physiological state of the other."[21,72–75] The resulting hypothesis is that as the bond between a human and an animal matures, both parties benefit. Evidentiary support for the human-animal bond conception for AAI in oncology is mixed: some investigated endpoints displayed post-treatment effects[8,11,28,29,31,39,58,76,77] while others have not.[8,11,25,31,54,58,77,78] Complicating things further, methodological design is not consistent across studies and studies are not yet directly geared towards elucidating the existence or effects of the human-animal bond. To date, the sole study to maintain the same animal-handler team throughout—a true test of the bond idea—observed mediocre effects: no significant changes in the intervention group after the study period.[31] Other studies that asked questions concerning patient attitudes towards pets largely found no significant correlation between these measures and the treatment outcomes of interest.[31,58,59,65,67,70,71,78,79] For prospective researchers, one troublesome aspect of this particular AAI conception is its necessitation of longitudinal studies that can allow a bond to fully develop, though tools like the Monash Dog Owner Relationship Scale[80] and the Lexington Attachment Scale can provide some indication of a bond's strength.[81,82] Additionally, the bond in question is a metaphysical phenomenon that cannot be interrogated directly and must be studied proximally through its effects. Fortunately, the human-animal bond is defined very broadly and in such a way as to account for most all of the aforementioned mechanisms implicated in causing cancer-related AAI's effects. Similar to the social support theory, this still diminishes the predictive capacity of the bond framework. Both Rehn et al.[83] and Hosey et al.[21] also raise an interesting point in their review of human-animal interactions work from AAI to working agricultural animals: there should be a fundamental, definitional distinction between human-animal bonds and human-animal relationships.[84] A relationship suggests some unspecified interaction with similarly unspecified effects for either participant but, the authors maintain, a bond indicates that a connection with a particular individual has been formed.[83,84] In other words, human-animal relationships would define a patient's positive interactions with therapy animals over the short or long term, but the human-animal bond would define a specific patient's mutual connection to a specific therapy animal—one that, for the patient, is not interchangeable with any other therapy animal similar to the relationship between an owner and their pet. However, as humans can form bonds

with multiple humans, they can likely form relationships and bonds with multiple therapy animals. Although Hosey et al.[21] raises excellent points, to avoid any potential confusion, we will continue to use the definition of human-animal bond set forth at the outset of this paragraph.

One should note that the human-animal bond and social support theories as defined by the researchers in cancer-related AAI are different in meaningful ways. Social support necessitates integration of the animal into an existing network that provides resilience to stress. Here, the therapy animal provides direct benefits to a subject while also improving that subject's interaction with other support nodes (e.g. nurses, doctors, and family members.) On the other hand, the human-animal bond theory does not require network integration nor does it insinuate any concomitant benefits beyond the human and animal in question. Rather, it suggests that the beneficial effects of animal-assisted interventions extend beyond coping with specifically stressful situations similar to cancer treatment and that these same effects can persist in other contexts ad infinitum as the bond strengthens. All this being said, these two theories most often cited by AAI researchers in oncology are not mutually exclusive and are likely complementary in producing the observed positive results.

Other Theoretical Frameworks

In this treatment of the main explanations of AAI's benefits in oncology, we must also mention the other ideas proffered by some researchers in the field: the self-object hypothesis, the cognitive activation theory of stress and the science of the unitary human.

The self-object hypothesis regards the therapy animal as an ideal object the human forms a stable attachment with.[85] Therapy dogs specifically improve a patient's life as they are non-judgmental and display joy when interacting with bonded persons.[70,86–88] This would generally mean that any positive AAI effects come from a better understanding of the self through interaction with the therapy animal. This is illustrated by Petranek et al.[68] who note that, before AAI sessions, patients can feel as if they are just their disease or as if they are passively waiting to be fixed by the attending medical staff. The authors thus argue that observed benefits come directly from patients' perception that participating in the study may be "doing something constructive or good for others and not just themselves." Johnson et al.[79] reiterates this point stating that AAT and complementary medicines in general help patients to exert control of their illness and their quality of life, resulting in a sense of active participation that produces positive effects. Essentially, patients can conceptualize themselves as more than their illness through interaction with the self-object of the AAI therapy animal. The greatest strength of this hypothesis is that it makes a clear affirmative case for the importance of the animal as a complementary medical treatment. For example, neither a therapeutic massage, a stuffed animal, nor chatting with a friendly stranger will utilize the specific psychological pathways of the self-object construction. Only a live therapy animal has all of the relevant characteristics to take on this role.

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Buettner et al.[89] make a case for the cognitive activation theory of stress as a way to understand AAI's benefits. This conception is based on general arousal and activation theory and focuses on specific definitions of stress in order to characterize and evaluate the effectiveness of reactions to stress.[89,90] Interestingly, Ursin et al.[90] notes that, "an essential element of cognitive activation theory of stress [is] that only when coping is defined as positive outcome expectancy does the concept predict relations to health and disease." For AAI, the cognitive activation theory of stress forms a psychobiological foundation.[89] Essentially, AAI is only useful to a patient under this framework in so much as AAI helps him to mediate his response to the stresses of cancer diagnosis and treatment. Buettner and colleagues thus designed the study with the aim of reducing cognitive stress loads while patients are in the cancer treatment waiting room.[89] While this theory somewhat resembles that of social support networks discussed previously, it presents a clearer pathway from overarching concept through to biochemical mechanism of action under its framework. Rather than existing as a generalized node in a fluid support network, the therapy animal directly alters the patient's stress response and the concomitant physiological correlates (like cortisol or heart rate) during a typical intervention.

Finally, Coakley and Mahoney[58] discuss the science of unitary humans and psychoneuroimmunology as an explanation of AAI's effects and their study's results. In this framework, organisms are considered as energy fields consisting of body, mind, emotions, and environment.[58,91] The psychoneuroimmunology component holds that "psychological variables have a direct effect on 'stress' hormones and that these, in turn, can modulate immune function and psychosocial well-being," somewhat similar to the cognitive activation theory of stress.[77,92] Thus, in AAI, the human's field interacts with and is altered by that of the therapy animal as the intervention proceeds. These interactions and energy alterations could then conceivably lead to reduced physiological stress and increased positive affect for both parties participating in the interaction. Although the science of unitary human beings has been met with some skepticism and valid critiques, this theory expands the conception of AAI beyond the two actors (patient and animal) involved in the therapy.[93,94] The main actors in the AAI are not just bodies, but also minds and emotions in a specific environment that impacts the actors' interactions. Part I of this review series also makes this case when contrasting group and individual therapies as well as private and communal treatment locations.[14] While still compatible with both the human-animal bond and social support network frameworks, neither theory explicitly accounts for how these kinds of environmental considerations may directly impact AAI outcomes.

Even though the aforementioned hypotheses have some explanatory power and predictive capacity for AAI, no researcher claims these to be complete. Additionally, the theoretical frameworks cited thus far are somewhat overbroad and generally derived from tangentially related fields. While this can be an appropriate starting and comparison point, the field will surely benefit from a detailed theoretical formulation unique to the constructs and idiosyncrasies of animal-assisted interventions.[95] Alternatively, multiple theories and frameworks can be knit together to fully explain AAI's range of effects. Noting the complex and potentially

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overlapping theories and mechanisms involved, it is possible that different hypotheses of action may be necessary for different sub-fields of AAI. For example, an autistic individual may receive general benefits from a therapy animal similar to those seen in patients with cancer, but also in a few ways unique to that class of conditions. While this makes the theoretical underpinnings slightly more complicated to parse, it does brighten the future possibility of targeted prescription of animal therapies to specific people in order to maximize positive effect.

Other Explanatory Concepts

Although we focus on the mechanisms and frameworks explicitly noted by AAI studies in oncology, other theories encountered throughout the human-animal and animal-assisted interaction fields should be briefly mentioned due to their relevance to the field.

Attentionis Egens

Humans and other species with advanced social systems evolved, among other things, "attention-need behaviors." This fact leads Odendaal[26] to put forth attentionis egens as a mechanism for understanding the human-animal interaction and its effects. Attentionis egens simply denotes the "need for attention on a normal, basic emotional level as the prerequisite for successful social interaction." Odendaal holds that the success of HAI is largely based on bi-directional attention-seeking behaviors where the therapy animal effectively assumes a role normally held by another human. A strong need for attention from the human leads to increased social behaviors by the animal, which in turn leads to a stronger human-animal bond overall.[26] Effective handling of the attention-needs leads directly to physiological changes (i.e. increases in typically affiliative neurochemicals) that mutually benefit humans and animals involved. This concept helps explain the successful inclusion of dogs into therapy environments such as cancer care. Dogs are highly social animals and can serve as an interspecies provider of attention and support for socially isolated or otherwise suffering individuals.[2] Attentionis egens may also explain why "friendly human" controls often appear to supply the same benefits to oncology patients as AAI sessions.[77,79] Attentionis egens is an interesting concept when juxtaposed with the increased human interaction mechanism. The latter holds that the therapy animal is a route to get more human attention, but attentionis egens says that the interaction with the therapy animal can, in itself, be a source of attention.

Sensory Stimulation

Physical touch and its benefits are conceivably just one of several sources of positive sensory stimulation provided by a therapy animal. In fact, some researchers argue that dogs can affect each of the senses to lower cortisol levels and engender "physical benefits including a decrease in blood pressure, heart rate, and respiratory rate."[32,96,97] For example, Nagasawa[98] found that owner's merely looking at their dogs was enough

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to significantly increase urinary oxytocin concentrations in both species. Similarly, Rehn et al.[99] found that the "mere reappearance of a person can elicit oxytocin release in dogs" that can last for a significant duration with physical affirmation. Though physical touch is the most thoroughly studied sensory stimulation paradigm, it is very conceivable that patients could—and likely already do—gain some additional benefit from seeing, hearing, and smelling the therapy animal in an AAI session.[96]

Responsibility/Task Completion

The next concept does not have a formal label but holds that completing defined tasks and activities with an animal can lead to positive benefits for the involved human. For example, a therapy dog could help a patient find a toy item or a therapy horse could work with the patient to traverse a riding course. In either scenario, the responsibility and cognitive burden for achieving the goal is shared by the patient and the therapy animal, either consciously or unconsciously. Another example simply includes the patient caring for and grooming the animal—a therapy component already included in many equine assisted therapy programs.[25,39,100] The additional benefits this responsibility concept offers—beyond the physical exercise or contact inherent to the AAI scenario—largely lie in the self-esteem boost inherent to taking on additional responsibility and the sense of accomplishment gained from successfully completing a task.[16,101]

Affection Exchange Theory

Affection exchange theory generally holds that "affectionate expressions often initiate and accelerate relational development" and are thus "key to human survival".[32,102] Briefly, there are five constituent postulates of affection exchange theory: 1.) humans inherently desire affection; 2.) feelings of affection are not always accompanied by expressions of affection; 3.) affectionate expressions aid human reproduction long term; 4.) individuals vary in affection need; and 5.) violating an individual's affection needs is deleterious.[32] With the exception of the third, this theory's tenets can be readily adapted to AAIs and, properly understood, many of these postulates even mirror other previously discussed concepts (e.g. biophilia hypothesis).[32] Thus, the mutual exchange of affection between patient and therapy animal would result directly in "enhanced physical and mental well-being experienced by AAI participants."[32] Affection exchange theory interacts well with the aforementioned social support hypothesis. Additionally, the fourth postulate is one of the few explanatory concepts that shed light on how animals with differing personalities may affect AAIs, rooting this in patient preference (i.e. preferring a calm therapy animal to an energetic one.)

Attachment Theory

An attachment is properly defined as an "an affectional bond with the added experience of security and comfort obtained from the relationship."[83,84] Much like the variation seen in parent-child attachments, human-

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animal attachments vary widely and should be investigated at the "individual [animal] level, rather than talking about the 'average' [animal.]"[83] The testable prediction for AAI in oncology, would be that the strength of the attachment and thus the quality of the overall bond correlates directly to the psychological and physiological benefits either party derives from the comforts of the relationship. However, until this point and for various methodological reasons, the research conducted in cancer-related AAI that also interrogated pet attitudes, ownership, and attachments did not find a statistically significant correlation to results. Other work in non-cancer human-animal interactions finds that closer relationships lead to stronger observed effects resulting from activation of the oxytocinergic system in both humans and dogs.[26,103] By analyzing an individual therapy animal's attachment and a specific patient's caregiving behaviors, attachment theory can be used to differentiate the quality of bonds under the broad human-animal bond framework after they have been formed.

Neurobiological Transduction Mechanisms

The mechanisms discussed to this point suggest an observable cause for AAI's effects but all deal with factors external to the human participant. Our understanding of how AAI generates positive emotions and effects would be incomplete without considering the neurobiological transduction mechanisms. This refers to the exact connections and pathways between proposed animal-assisted interaction mechanisms and the observed physiological or psychological outcomes, all following from the overarching frameworks [**Figure 1**]. Previously, we mentioned Odendaal and colleagues' work elucidating the biochemicals released during affectionate contact between humans and animals.[48,104] They found that affectionate human-dog interactions positively impact dopamine, cortisol, oxytocin, prolactin, endorphin, and phenylethylamine concentrations in both humans and dogs. Moreira et al.[27] also cites the release of endorphins and adrenaline in the bloodstream as a reason deeper than the distraction mechanism for AAI's positive effects. They further maintain that these biochemicals are the actual physiological correlates and links to their observed result of decreased heart rate variability post-intervention. Further supporting this idea, Johnson et al.[79] generally note that interacting with an animal has effects in the body that are psychological, but that also play into a feedback loop with the endocrine and immune systems.

Although much of the work on the biochemicals that actually produce the effects noted with cancer-related AAI has focused on the physical touch mechanism, the idea of neurobiological transduction extends to all the other mechanisms as well.[26,48,103,105,106] In other words, the tenets of each framework allow for the interplay of certain mechanisms and these mechanisms in turn directly affect the neurobiology of the patient [**Figure 1**]. For example, the physical touch mechanism requires recruitment of a sensory neural pathway—in this case touch—before the brain can process the positive physical stimulation and the situational context (i.e.

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the AAI session). From here, the brain naturally responds by releasing dopamine, epinephrine, and other neurochemicals, resulting in a betterment of mood and a generally positive affect.[26,48,104] This example transduction pathway would be significantly different than that employed when exercising with a therapy animal via the movement mechanism. Here, the factors impacting the patient's positive affect would stem from the positive benefits of exercise and the neurochemicals it releases. Similar theoretical pathways can be postulated for each remaining mechanism—with the possible exception of compatible animal personality. The transduction pathways may ultimately end in the release of similar sets of neurochemicals, but the pathways to their release are slightly different for each mechanism. In the future, this conception of neurobiological transduction may be a potent way to differentiate the effects of certain mechanisms that make up a framework. Again, while both may lead to release of dopamine, physical touch versus therapy animal gaze must traverse different biochemical pathways to achieve the same positive effect. With properly constructed AAIs, diligent researchers could isolate each mechanism and its pathway, improving our understanding of certain frameworks and clarifying how the mechanisms interplay. Gee et al.[51] notes that different therapies may be effective for different kinds of stressors so the neurobiological transduction idea also opens the door for targeting types of AAI to the different needs of cancer patients. The concept of neurobiological transduction may also help to differentiate which mechanisms provide direct psychological benefits without taking a detour through a certain physiological pathway. For example, some mechanisms, such as touch or exercise, clearly rely on physical transduction pathways while others, such as therapy animal gaze, merely require the human to see the dog and psychologically recognize the positive benefits. However, it is likely that there is a complex regulation of biochemicals within a mechanism's delineated neurobiological pathway and that the causality within the system is not straightforward.

This said, there is a viable candidate for a unifying AAI neurochemical and Beetz et al.[107] makes a compelling case that all of the beneficial effects of AAI are likely the products of stimulating the oxytocinergic system specifically. Johnson[96] also support this explanation, implicating cortisol as a major actor alongside oxytocin. For Beetz et al.[107], all of the mechanisms and the related transduction pathways aim to release oxytocin, leading to every AAI benefit observed (e.g. decreases in depression, increases in oxygen saturation). This theory is eminently plausible as oxytocin is well understood to be the "bonding" or "affiliative" neurochemical peptide.[108–111] Additionally, such releases of oxytocin can still affect outcomes in short term positive interactions, explaining AAI's efficacy in interventions with short durations, low frequencies or both. Oxytocin as the neurochemical of final interest also explains certain observed gender-specific AAI effects (e.g. women's oxytocin increasing after pet dog interaction whereas men's oxytocin decreases.)[82] Furthermore, oxytocin is known to inhibit the release of cortisol and thus could play a significant, direct role in the patient stress reduction observed. Beyond postulates about the role of oxytocin, a precise biochemical pathway with

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clear neurological candidate peptides for AAI's observed physiological effects in patients and therapy animals alike has not been fully delineated.

Conclusions

Discussion of Theoretical Limitations & Suggestions

To address many of the non-methodological limitations of the AAI field in oncology, AAI in oncology and pet therapies generally require a more rigorous treatment of the theoretical aspects of the phenomenon and the concomitant explanations of results this can provide. Ideally, as a few researchers have,[58,89] the norm would be starting from the highest theoretical level and then designing an experiment to evaluate one's predictions. Researchers with various hypotheses in the AAI space would thus have clearer and, importantly, more connected experimental paths. This would also allow researchers to effectively tackle problems such as determining when a stable, human-animal bond has formed or identifying exactly which physiological or psychological parameters are most relevant to AAI in oncology. Additionally, deriving studies from a larger theoretical substrate can greatly improve control condition designs as the latter would necessarily depend on the intervention's proposed mechanisms of action.

Most work in the AAI field has not yet considered the therapy animal's perspective and the positive or negative effects (such as increased animal stress due to rough handling, for example) that AAI can have for them.[21] As such, the field's efforts could also benefit from the development of theoretical frameworks recognizing that the nature and outcomes of treatment for humans will likely vary directly with the state of the therapy animals involved. In fact, mechanisms of action that directly address how AAIs impact the therapy animal in the near- or long-term would be an additional boon to the field. More data from this perspective in hand, researchers could also know whether or not AAI is a zero-sum game with one-sided benefits for humans—an outcome in stark opposition to the human-animal bond hypothesis and many other proposed frameworks.

Our discussion of the theoretical frameworks focuses on hypotheses advanced by the AAI papers in oncology and includes a brief treatment of other relevant concepts in the human-animal interactions literature. From this, it is clear that there is tremendous overlap in the theoretical concepts put forth to account for human-animal interactions and animal-assisted interactions' effects. This overlap—coupled with patterns in observed psychological and physiological outcomes—strongly suggests that future work may evolve into a unified conception of AAI. At the moment, of the few researchers who even consider the theoretical implications of their work, many do not consider if their results have multiple mechanistic explanations or fit under multiple frameworks.[21] Here, the aforementioned significant overlap of theory prescriptions in AAI means that some

results can just as easily be described by a framework different from that implicated by a researcher. This is not a critical limitation for the field or for the prospect of a unified theory. When implicating certain explanatory concepts, special attention should be paid to results that either effectively support the named concept to the exclusion of all others or, when considered as a whole, closely reflect the named concept's tenets.

Theories in the AAI field appear to implicitly account for the effect of the environment-on patient outcomes, but this may not be sufficient. It is conceivable that many treatment environment decisions have observable effects on patient outcomes and animal welfare. For example, delivering AAI sessions in a patient's hospital room may boost patient comfort levels—important to the attachment theory. However, AAI sessions in a designated therapy space may increase a patient's ability to exercise and physically interact with the therapy animal—important to the movement mechanism. Other examples such as indoor versus outdoor treatment and one-on-one versus group animal therapy could have constructive or destructive impacts on various AAI mechanisms of action. Researchers rightly tailor their treatment strategies and protocols to the needs of their patients, but study design should also consider the implications for theoretical mechanisms and the related effects on clinical outcomes.

Another theoretical limitation that is not easily resolved relates to the accepted definition of success in AAI. As many authors note, the AAI field does have methodological weaknesses that challenge the validity of certain claims or produce effects in clinical endpoints that are not statistically significant.[15,18,19,112] However, these results may still be clinically significant and the general acceptance of anything that helps cancer patients even somewhat may also be valid. Wilson[112] specifically provides the analogy to drugs in medicine that "do not have a statistically significant effect upon a given patient sample" but still "lower blood pressure, heart rate, or cholesterol"—without side effects—in a clinically significant way. The AAI field in oncology should certainly adopt various methodological best practices to provide for high quality results. However, the field should potentially also take appropriate consideration of statistically insignificant results that, "upon more critical review, may well be clinically significant."[112] While researchers in cancer-related AAI are not all pursuing the same treatment goals beyond improved patient quality of life, if any at all, lenient and inclusive definitions of success provide for more combinatorial treatment paradigms.[113] As an example, the same patient can benefit from therapy animals in waiting rooms before his radiation therapy sessions[78], during cancer-related counseling[67], as well as during the recovery period following cancer remission.[39] To be useful, theoretical frameworks must be able to account for the known effects of a patient's stage of cancer and clinical treatments when combined with animal-assisted interactions.

Summary and Conclusion

In Part I of our two-paper systematic literature review series, we presented the results of a systematic literature review evaluating the designs and efficacy of animal-assisted intervention studies in oncology through quantitative metrics. Here in Part II, we provided a discussion of the mechanisms of action proffered by researchers to explain the observed experimental results before briefly discussing a few other relevant ideas throughout the animal-assisted interactions field. These mechanisms included compatible animal personalities, pleasant tactile contact, physical movement, novel distraction, and increased human-to-human interaction. These mechanisms overlap and interplay within overarching theoretical frameworks of which the social support network and human-animal bond concepts are the most prominent. Some researchers also invoked other ideas such as the self-object hypothesis, the cognitive activation theory of stress, and the science of the unitary human when discussing their work. We also attempted to connect frameworks and mechanisms to the observed psychological and physiological outcomes by discussing the known neurobiological transduction methods and the critical role of oxytocinergic systems in AAI.

While AAI work in general and in oncology has room to grow, the field has significant promise to positively impact patients' quality of life. Future studies should actively incorporate and test solid theoretical frameworks based on quantitative observations to advance the field's understanding of AAI in oncology. For cancer-related AAI specifically, researchers should also consider experimental outcomes achieved in related sub-fields (i.e. AAI's benefits in recovery from non-cancer surgeries likely apply somewhat to recovery from oncological surgeries.)[29,114,115] The concepts discussed in this review can help researchers to focus on elucidating the effects of one mechanism, to maximize benefits for patients by combining several mechanisms, and to attempt everything in between. All things considered, the AAI field is especially poised to make significant progress towards a unified theoretical framework and, more importantly, towards effectively treating cancer patients in a holistic way.

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