

Original Research

Intranasal Insulin in Alzheimer's Disease: A Pragmatic Account

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OBM Geriatrics
2019, volume 3, issue 3
doi:10.21926/obm.geriatr.1903069

Received: March 15, 2019
Accepted: June 06, 2019
Published: August 13, 2019

Abstract

Pragmatic competence includes the capacity to express illocutionary force and successfully achieve perlocutionary effects, in order to guarantee fully functional communication exchanges. Improved pragmatic competence in patients has been found in patients with Mild Cognitive Impairment (MCI) and early to moderate Alzheimer's Disease (AD) in the domains of jokes, self-expression and empathy after extended, targeted intranasal insulin therapy. In this paper it is argued that extended intra-nasal insulin treatment can even significantly augment the use of illocutionary and perlocutionary abilities in the areas of humor, irony and sarcasm in later stages of AD. The pragmatic capacity to relate emotionally to others in conversation with humor that can cause laughter can reduce the social isolation of AD patients from other speakers, enhance opportunities for meaningful conversation and lessen the caregiver stress.

Keywords

Pragmatic competence; intranasal insulin; Alzheimer's disease



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1. Introduction

Intra-nasal insulin has been proved to be useful for the treatment of patients with several neurocognitive deficits: McIntyre et al. [1] evaluate the effect of intra-nasal insulin on neurocognitive function in euthymic patients with bipolar disorder and found a significant improvement on executive functions following an eight-week administration of intra-nasal insulin combined with placebo; while Brabazon et al. [2] assessed intra-nasal insulin treatment after traumatic brain injury (TBI), which results in learning and memory disfunction. Results show patients' improvement of memory, increase of cerebral glucose uptake and decrease of neuroinflammation and hippocampal lesion volume. A similar finding was reported by Ritze et al. [3] on healthy men: memory improvement following 8 weeks of intra-nasal insulin delivered in four daily doses of 40 IU (cf. Hamidovic [4] for a contrary view in abstinent smokers). Improved pragmatic function in patients with Mild Cognitive Impairment (MCI) and early to moderate Alzheimer's Disease (AD) after targeted therapy has been the subject of several studies [5-7]. Accumulating evidence suggests the capacity of the short-term administration of intra-nasal insulin to improve verbal fluency and to slow cognitive decline in the areas of immediate recall and list learning recall in adults with MCI and early AD [8, 9]. The long-term use of intra-insulin in MCI and moderate AD has been shown to improve scores on face and affect matching tests, to stabilize language fluency tests and to significantly improve executive functioning and visuo-spatial skills [5]. Extended intra-nasal insulin also improved pragmatic competence in the domain of jokes, self-expression and empathy in patients with MCI and moderate AD [6].

This article finds that intra-nasal insulin treatment significantly augments the use of humor, irony and sarcasm even in later stages of AD. Employing a model of pragmatic competence [6], we show the ability of a late-stage AD patient under long-term, targeted treatment to use self-deprecatory humor, sarcasm and metaphor in multiple inter-personal settings. We claim that the ability to recognize and tell jokes requires continued pragmatic competence because the speaker needs to assess the reaction of the addressee and to understand the meaning underlying the relevant discourse utterances to be then able to flout the conversational maxims to make a joke [7]. The pragmatic capacity to relate emotionally to others in conversation with humor that can cause laughter reduces the social isolation of AD patients from other speakers. Improved communication, in turn, enhances opportunities for meaningful conversation [10]. This can lessen the caregiver stress that is often endemic in AD which is the result of low levels of real communication with the patient [11, 12]. The continued pragmatic capacity of a late-stage AD patient to use humor in socio-interactive environments further suggests that several aspects of pragmatic competence in AD could be independent targets for therapeutic improvement in their own right.

The paper is structured as follows. In the next section, we outline the importance of performatives, specifically of illocutionary and perlocutionary acts, in our model of the functioning of pragmatic competence under cognitive impairment by AD and its improvement under specific treatment. Section three outlines the use of humorous, sarcastic, ironic utterances as speech acts. Section four to five detail the pragmatic competence and the use of self-deprecatory humor, sarcasm and metaphor of a late-stage Alzheimer patient under targeted treatment. Section six draws several conclusions with respect to the relevance of pragmatic competence under treatment. Specific reference is made to perfusion studies of the nose-to-brain pathways of intra-

nasal insulin in the functional neuroanatomy of humor in AD comprehension and pragmatic inferential reasoning.

2. Pragmatic Competence in AD under Targeted Treatment

Our model of the functioning of pragmatic competence under cognitive impairment by AD and its improvement under specific treatment incorporates pragmatic units as specific speech utterances [6]. Using Austin's [13] conception, of performatives, these utterances can be understood as speech acts which are considered to "do something", in other words, to perform acts of different sorts: apologize, thanks, name, marry, etc. Such speech acts which perform actions can be contrasted with language use whose function is to describe states of affairs (constatives) [6]. Thus, by pragmatic competence, we refer more generally to the study of linguistic utterances and their association with the speaker and addressee's intentions, plans and beliefs. This incorporates cognitive and social concerns into central stage of pragmatic theory [14].

Specifically, our model examines *three* acts related to an utterance. These include the "locutionary act" or the act of saying something meaningful, the "illocutionary act" (the act performed in saying something) and the "perlocutionary act" or effect that emerges as the consequence of saying something. Improved illocutionary capacity also refers to the ability to express and to look for an effect of that expression of a speech utterance. The effect that a person might want to achieve thorough a specific communication interaction can include validating the other person's feelings, agreeing with another's feelings, expressing empathy for the other person, expressing solidarity with another and/or even to reduce the amount of perceived psychic pain caused by disappointment.

Performatives utterances only do something when uttered in the "appropriate circumstances". For an utterance to have the intended (perlocutionary) effect, the speaker must express sincerity (intention) and to use words appropriate for the circumstances. This refers to "felicity conditions" or those conditions which have to be satisfied in order for a performative utterance to be satisfactory. As Schatz & González [6] note: "These felicity conditions are not equal, and their violations are also dissimilar. Violations of some conditions result in misfires, when the intended action is not performed. Felicity conditions can be verbal or non-verbal. The first ones relate to the uttering of certain conventional words; non-verbal ones are related to the procedures itself, the appropriate participants, etc." Typically, this is especially challenging to the pragmatic capacities of people living with severe Alzheimer's disease where language deterioration results in multiple communication problems associated with "retrogenesis".¹

¹ Retrogenesis is argued to be the process by which "degenerating mechanisms in the brain, as found in AD, reverse the order of acquisition of functions in normal child development, and constitutes the theoretical background for the notion of old age being a second childhood held by poets and playwrights since antiquity, e.g. Aristophanes and Shakespeare [15, 16]." The concept of retrogenesis has been used in the fields of function, cognition, emotion, neurology and neuropathology [16, 17]. Linguists frequently cite such studies to describe language deterioration in dementia with reference to the clinical stages of early, middle and late dementia [18, 19]. A brief summary of these staged communication problems are early stage dementia--difficulties in word finding, in understanding and producing complex sentences, and in maintaining topics in conversations; middle stage--the amplification of these problems and the communication of individuals with dementia becomes empty and ambiguous, with poor comprehension and many repetitions [20]. By the late stage, it is often assumed that little understandable language is used with no testable comprehension.

After targeted intra-nasal insulin treatment in persons with MCI and early to moderate AD, we documented how patients were better able to express how they felt, increasingly capable of engaging in social conversations and capable of expressing appropriate opinions in conversation. This improved illocutionary capacity, in turn, had immediate positive perlocutionary effects on their listeners (wives, friends, doctors, caregivers) who expressed pleasure that the patients were now so “present”, “happier”, “fluent in language use” and “demonstrated good quality of life” [6]. This model thus considers pragmatic units not only as utterance elements, but also as units incorporating cognitive and socio-interactive dimensions, which are essential in the determination of the success of the perlocutionary and illocutionary functions associated to speech acts.

More broadly, pragmatic functions (of the illocutionary or perlocutionary type) refer to the set of inferential processes, strategies, arrangements, and constraints regulating illocutionary force and perlocutionary effects for speakers [7]. These types of pragmatic functions can be partly understood as belonging to executive-function mechanisms in general. McDonald [21] considers pragmatic inference generation and executive function as similar processes, given that “increasing degrees of impairment in the executive system correspond to greater and greater impairment of inferential reasoning.” In addition, both executive function and inference require simultaneous attention and the processing of multiple sources of information in parallel. Executive function is by definition “associated with the various cognitive, linguistic and sensorimotor elements in the intrapersonal domain over which it exercises control [7]”.

3. Self-Depreciatory Humor, Sarcasm, Irony, Metaphors & AD

Self-depreciatory humor or black humor has been precisely understood within the context of Austin’s three-part model of speech acts. Kitazume [22] argues that the locutionary act is the uttering of the speech (the humor itself) and the illocutionary act is the arousing of laughter and self-deprecation. The perlocutionary effect (or the effect of the utterance on others) of self-depreciatory humor in terms of Austin’s speech acts can be understood as follows:

The perlocutionary act is the effect of self-depreciation, which lowers the assessment of the speaker, while it gives a superiority feeling to the hearer. However, the devaluation is moderated by the effects of laughter and minimized when the context of weakness is an already known fact with little informational value...

Self-depreciatory humor can also have the perlocutionary effects of, variably, deterring aggressiveness, achieving appreciation, sympathy and even love, enabling a person to grapple actively with the fear his/her weakness arouses in him/her, dispelling the fear of others and/or to cheer up others. It can also function as in a defensive way, to protect a person from negative experiences and/or as a tension release to cope with death [22].

Sarcasm has mostly been defined as a severe form of irony often intended to insult or wound, i.e. associated with negative psychological effects [23]. Nevertheless, the use of sarcastic, self-mocking humor has recently been found to be “indicative of high scores in psychological well-being dimensions such as happiness and, to a lesser extent, sociability” that can come from laughing at oneself [24]. Metaphors (such as “life is a journey”) are used to express an idea by referring to something else in a non-literal way. Taken literally, metaphoric statements are mostly wrong [25]. The meaning of a metaphor is suggested through association and comparison of similarities between different expressions that are not stated explicitly. Sarcasm, irony and

metaphor are figurative utterances that can be considered to be the indirect performative of a single utterance by way of performing another [26]. As Bach [27] notes “When an illocutionary act is performed indirectly, it is performed by way of performing some other one directly. When an utterance is nonliteral, as with likely utterances of “My mind got derailed” or “You can stick that in your ear,” we do not mean what our words mean but mean something else instead”. Although unexpected occurrences of sarcasm and irony have even been documented in patients with moderate to severe AD [28, 29], it is often assumed that people with dementia lack the pragmatic competence to even understand either and “will be confused or even hurt by the intent if others use it” [30, 31]. This lack of pragmatic competence is often assumed because irony and sarcasm require high cognitive load and decline with age and AD disease stage [23, 32, 33]. Metaphor use and interpretation in AD importantly relies on executive functioning skills such as inhibition, abstraction and the computation of meaning typically not associated with late-stage AD [33, 34]. Successful metaphor interpretation in AD relies on the speaker’s continued abstraction abilities, e.g. the ability to abstract away from literal meaning (compute related predicates) [34].

Wray [12] contends that dementia, and the several variants of Alzheimer’s disease, may constitute a privileged field to test the decay or preservation of pragmatic competence. Dementia not only significantly affects the patients’ cognitive and pragmatic abilities but also has concrete, measurable effects on their families and other individuals professionally or socially involved with them. As such, it allows for an ideal “testing ground to witness the interaction of linguistic behavior with other interactional components in a more general cognitive and social environment” [6]. Section four now provides the medical and neuropsychiatric test history of a late-stage AD patient on extended intra-nasal insulin treatment. This next section also details the discursive analytic frame [35, 36] used to understand the communication between the patient and his caregivers in comprehensive, open-ended, naturalistic conversations [37]. As Hamilton [38] notes, the “interactiveness of communication, with the contribution of the non-demented conversational partner is crucial to successful conversation”.

4. Patient History, Intra-Nasal Insulin as a Targeted Treatment & Methodology

The patient (“AR”) was an 88-year-old former teacher being treated by a Kaiser Permanente Neurologist who diagnosed him with Alzheimer’s Disease in December 2012 after a May 2012 diagnosis of Mild Cognitive Impairment. By March 2013, he was evaluated by a UCSF neurologist and met the criterion for moderate probable AD and was administered a complete neuropsychiatric battery (March 2013) and annually (March 2014, June 2015). The patient was also involved in the compassionate use of twice daily intra-nasal insulin for the purposes of reducing cognitive decline which began 6/13 and increased to three times daily (September 2017-December 2018). This treatment was administered by nurses who also gave him his daily medications and reminded the patient to conduct daily or weekly hygiene (bathing, tooth brushing, correct dressing). The patient ate independently without assistance. The patient’s finances and medical management were done by his daughter. The patient was able to live independently in his home with the aid of his elderly girlfriend (2012-2017) then was placed in an Alzheimer’s assisted living facility when she became ill (November 2017-December 2018). The patient died unexpectedly from acute heart failure after hip surgery from a fall in December 2018.

As untreated, AD is a “devastating disease” [39]. The promise of intra-nasal insulin as a therapy to improve the cognitive capacities and quality of life for AD sufferers, their caregivers and families has been around since 1989. It was first proposed as a non-invasive intranasal method for bypassing the blood-brain barrier (BBB) by William H. Frey II and later expanded for the specific use of intranasal insulin to target the brain to treat Alzheimer's disease and other CNS disorders [40, 41]. In 2015, as an AD therapy, it was demonstrated to be safe in multiple, double-blind clinical studies with minimal side-effects as substantiated by currently available MRI brain imaging data and positive cognitive testing results on over 100 Alzheimer patients published in several peer-reviewed journals [9, 42] (see Supplementary Information). Currently, it is in stage II/III of FDA review with 240 patients (The Study of Nasal Insulin in the Fight Against Forgetfulness (SNIF 2018) (www.clinicaltrials.gov, identifier--NCT01767909) [43].

At MCI diagnosis (5/17/12), patient's CT brain scan showed no significant intracranial pathology and aging brain morphology [5]. By 4/12/18, five and a half years after AD diagnosis and five years after starting intra-nasal insulin treatment, CT scan showed “likely considerable” temporal lobe and frontal lobe volume loss and, consistent with AD volume loss²” (but not necessarily with function loss) [44]³. The doctor's discussion with the daughter of the patient after physical exam and the 4/12/18 CT results revealed that while his brain showed volume loss consistent with late-stage AD, the patient was still “very functional with good language skills” and, to the doctor's surprise, the patient still possessed “the body of a 70 year-old” [48].

Schatz & González [5] present treatment-mediated improvements in language, visuospatial and, in particular, executive functioning test scores of AR at moderate AD and an early MCI patient under targeted treatment. In the area of language skills, these data show two-year improvements in AR's Delayed Story Recall Score, Hopkins Verbal Learning Test [HVLTL], the Boston Naming Test [BNT], PPVT and WRAT [2014-2015] [8, 9]. The HVLTL reflects frontal lobe functioning [49]. In the area of visuo-spatial skills and working memory/executive functions, his annual rate of decline was significantly (not marginally) slower than those reported in the literature for patients with comparable MMSE scores [50]. These data showed annual improvement and/or lack of deterioration in Digit Span, WORLD, Calculations, Pentagons, Modified Rey and Face Matching [5]. In AD, Zhao, Zhao, Ding, Teramukai, Guo, Fukushima & Hong [50] found that while executive and

² CT Head Report without Contrast: “Lateral ventricle were enlarged, with disproportionate enlargement of the frontal horns. Temporal horns are both markedly enlarged, more so on the right. Third ventricle is moderately enlarged. Basal cisterns are enlarged, as are the sylvian fissures. Overall, findings are compatible with generalized volume loss, with disproportional frontal and temporal lobe volume loss. This includes medial temporal lobe volume loss with likely considerable hippocampal volume loss especially on the right. There was no intracranial hemorrhage, large territory infarct or other acute intracranial abnormality identified. No extracerebral collection.” The patient's CT also showed moderate microvascular/small vessel disease. In terms of the patient's functional symptom loss over time, by 4/16 he needed more extensive assistance with bathing and dressing and by 4/18 patient became incontinent. Patient was also not able to recall most details of his personal history, although he had very limited recall at baseline before intra-nasal insulin began. The patient did not wander or show any major personality changes such as depression [5]. Until the final days of his life, he was also still able to eat independently with some assistance cutting up his food.

³ For a complex discussion of how intra-nasal insulin is transported from the nasal cavity to the central nervous system including the cerebral cortex, which is bathed by cerebrospinal fluid (CSF) and the gray matter, via both olfactory and trigeminal pathways, see Abimbola, Akintola, van Opstal, Westendorp, Postmus, van der Ground & van Heemst [45]. It is the functional effects of insulin on certain brain areas that are hypothesized to have beneficial effects on brain function including memory and cognition [46, 47].

visuo-spatial rates typically deteriorate at a faster rate than all other cognitive dimensions, the average annual decline in attention rates was even more pronounced, registering a negative decline 156.04% per year. In contrast, both AR and the early MCI patient either significantly slowed (AR) or even reversed (early MCI patient) annual cognitive decline as measured by neuropsychiatric batteries covering memory, executive functions, attentional span and visuo-spatial skills [5]. Prolonged attention span was found across patients with Phelan-McDermil Syndrome after 1 year on intra-nasal insulin [51].

4.1 Discursive Analytic Frame

The data used in this paper came from audio recordings of everyday conversations between AR, his caregivers, family members with the researcher present and nursing home staff (nurses, aides, occupational therapists) in the patient's rest home. Data consisted of conversations during daily interactions (during care routines, walking exercises and activities) and observational notes made by the researcher on non-linguistic signs and the context. AR often involved his caregivers in the conversations which were analyzed as part of the communicative interaction.

These interactions were analyzed using Schiffrin's [35, 36] discourse analytic frame for the study of utterances as social interaction. Schiffrin [36] developed a frame of five components for studying discourse: exchange structure (turn-taking); action structure (organization of speech acts, among them the use of humor, irony and sarcasm); ideational structure (the relation between propositions or ideas); information state (the organization of information and knowledge, what the conversational partners possess and what they share); participation framework (how conversational partners relate to each other and to the situation in what they say and do). Communication interactions were principally between AR and his daughter, his main caregiver—ST—and members of the nursing home staff. Section five presents now the data on AR's use of self-depreciatory humor, sarcasm and metaphor under targeted treatment.

5. Humor, Sarcasm & Metaphor & its Pragmatic Effects under Targeted Treatment

5.1 Verbal Games

His daily care-giver, ST, plays a frequent verbal game with him. As they walk toward his room door which has AR's name tag located on it, ST often turns and asks him in a playful tone: "Who is that"? to which the AR mainly responds "Ta da—that's me". One day, he answers with retrieved German and says: "Das est me"! ST, in later recounting this vignette to AR's daughter, noted how great that was that he could even retrieve those German words. Then she said: "It sure beats his bitching".

5.2 Playful Humor

AR's daughter, upon passing her father's name tag on room, tests her father by asking the question: "Who is that"? with a tone that implies she does not actually know who that person is. Her father immediately looks up at her and says in surprise: "Don't you know"? and then realizing at that moment that she is teasing him, he joins the joke and makes the playful comment: "I wonder who that is?"The daughter then laughs.

Both of these conversational vignettes show the patient's continued capacity to receive and make jokes. They demonstrate the illocutionary and perlocutionary effects of humor on both the patient and his caregivers. In the first instance, the caregiver initiates the conversational exchange by asking the patient "Who is that?" The patient, still able to recognize his own name and identity, answers correctly "That's me" but also responds with humor ("Ta da") and is even able once to retrieve from memory the German version of the expression ("Das est me"). In this first pragmatic exchange, the patient is able to have a positive perlocutionary effect on the listener ("It sure beats his bitching").

In the second exchange, the patient is able to express surprise that his daughter doesn't appear to recognize his name ("Don't you know?"). Immediately thereafter, however, when he recognizes she was teasing him, turns the joke back around ("I wonder who that is?" ...). This latter statement--an illocutionary act or the ability to express and to look for an effect of that expression--then has the intended positive perlocutionary effect of causing the daughter's laughter. This communication interaction also shows AR's continued pragmatic ability to correctly analyze and verbally respond to social context.

5.3 Humor Used to Assert Autonomy

Moss [37] found that late stage Alzheimer's patients did very occasionally employ sarcasm when the situation was unbearable to them, when they wanted to change the situation and when care-givers were intruding on their privacy and autonomy. In open-ended interviews with patients in naturalistic settings, for example, one patient "Sigrid" with late middle stage AD, was able to use sarcastic understatement in an intelligent conversation with a caregiver. And in another instance when being pressed to get up out of bed by a caregiver who then got summoned to another room, Sigrid employed direct sarcasm, saying to her caregiver with an angry and biting tone: [go] "so you can go and do what you are good at" [30]. For Fabricius and Roksvold [52] and Lindhardt [53], the aim of humor used to assert autonomy and/or ironical utterances is to influence the conversational partner to share one's view of the topic of conversation and change the situation.

In the following pragmatic exchange at AR's nursing home, his daughter has to get her father to put daily ice on his swollen, injured hand which he does not want to do. She sits him down at a group table with other AD residents before she leaves the nursing home. Two female residents with mild to moderate AD are already sitting at the table when AR's daughter seats him.

Daughter: "You need to put ice on your hand." She then applies the bag to his hand.

AR: "No, it is too cold".

Daughter half-pleads/half-admonishes him: "You need to keep this ice on—just for 5 minutes."

AR turns to the ladies and says: "Damn, 5 minutes—I just can't get rid of it" [referring to the ice]. Other residents laugh at the joke.

In another instance, the daughter is leaving the rest home and sits her father in a chair in front of a Christmas tree being decorated by the nursing home cook who is up on a ladder hanging decorations on the tree. The cook, who is always eager to assist with this patient, asks him:

"Do you want to help me get up here to hang the decorations?"

AR quips: "No, and don't expect me to help catch you if you fall."

Cook: Laughs

These conversational exchanges show how jokes are employed by the patient to achieve the intended perlocutionary effect on the addressee(s) (laughter). In the first instance, however, AR is also using a joke in an attempt to arouse sympathy in others and to protect himself from a negative experience. AR clearly would prefer not to have to feel the coldness of the ice on his hand and thus initially refuses the ice (“No, it is too cold”). When pushed by his daughter (“It is only 5 minutes”), AR relents but expresses his frustration in a joke to his fellow residents (“Damn 5 minutes—I just can’t get rid of it”). In the second exchange, AR shows strong self-awareness of his own physical limitations and is able to use a sardonic tone along with his words (“No, and don’t expect me to help catch you if you fall”) to protect himself and the cook against a potential accident. In both instances, the AR is showing self-awareness of his own limitations and using humor to have its intended perlocutionary effect on others (laughter) in dealing with intrusions on his autonomy by caregivers.

5.4 Sarcasm

In the following communication exchange, AR’s daughter is helping her father to prepare himself to receive an award with other veterans for the 2018 Veteran’s Day. In this upcoming ceremony, AR is required to shake hands with a military officer to acknowledge the receipt of the award and his daughter wants to prepare him for a public event where he is required to perform. Daughter: “Today is Veteran’s Day—and they are going to celebrate those people who were in the military. Do you remember you were in the military—in the Korean War”?

AR: “Not so well” [His tone suggests he is still aware that he should be aware].

Daughter: “Well, you were, you read the radar screen and radio, but you were not on the front lines”.

AR: Sarcastic tone: “Well, *that’s* good.”

Here AR is displaying sarcasm. On one level, AR is directly stating that it is good he was not in danger on the front lines of war. This implies the cognitive capacity to recognize the danger of a war context on the front lines despite the fact that AR could not remember having served in the Korean War. Yet, several elements of the conversation---the context---that he will be receiving an award for bravery in military service, AR’s empathic tone (*that’s* good) and his use of the pragmatic discourse marker “well” imply otherwise. As Blakemore [54] notes, the use of “well” as an utterance often implies “the speaker’s belief that certain assumptions are not manifest to the hearer”. And, as Inness [55] notes, these can include utterances that are unpalatable in some way to either the speaker or the hearer. In this utterance, AR appears to employ the illocutionary act indirectly [26, 27], using a pragmatic discourse marker and tone, to convey the message that he is actually glad that he was not in direct danger even though that would not be potentially honorable in the military’s ceremonial context.⁴

⁴ To be sure, in sarcasm, speaker attitude and the affective relationship with the listener (like-dislike) matters in influencing interpretation. A “like” relationship lends itself more to the listener interpreting a literal comment non-literally as sarcasm or banter [21]. In this instance, AR’s daughter had also repeated this conversational interaction about whether her father remembered his service in the Korean war and that he served as a radio operator near, but not on, the front lines on a different day and received the same response ‘Well, *that’s* good’.

5.5 Self-Depreciatory Humor Used to Achieve Sympathy & Illocutionary Capacity

Self-depreciatory humor can have a series of functions including deterring aggressiveness, achieving appreciation, sympathy and even love, enabling a person to grapple actively with the fear his weakness arouses in him, dispelling the fear of others and/or to cheer up others. It can also function as in a defensive way, to protect a person from negative experiences and/or as a tension release to cope with death [56]. The following conversational exchanges illustrate how AR is able to employ self-depreciatory humor with the illocutionary capacity to achieve the perlocutionary effects on the listener of humor and even sympathy.

Walking down the hall in his nursing home one morning with his daughter, AR encounters a nursing aide who asks him: “How are you AR?” He replies: “Half-asleep” and then laughs and the nursing aide laughs.

One afternoon, his daughter arrives and attempts to get her father to rise up from sitting in a chair which is difficult for him because of his injured hand.

She says to him with some impatience: “Are you coming?”

AR answers: “I am coming—slowly but surely, mostly slowly”.

On another occasion, after doing his daily posture exercises against the wall to improve his stooping posture, AR’s daughter reminds him to, and mildly castigates him for, not keeping his head up against the wall and to walk upright to which he replies:

“I am doing the best I can—which ain’t much, but that’s life”.

In these two initial instances, AR is using self-depreciatory humor to respond to caregivers who are concerned about his well-being and to grapple with his weakness (tired, slow to rise from the chair) in humorous ways. AR also employs self-depreciatory humor in a more self-defensive way to protect against his daughter’s mild castigation of him (“I am doing the best I can—which ain’t much but that’s life”). This utterance sends the message that he is doing the best he can even though it is limited. In turn, this has the perlocutionary effect on the daughter of eliciting sympathy for him and of not criticizing or pushing him harder to do exercises that are challenging.

The capacity to achieve sympathy as a perlocutionary effect relates to illocutionary capacity: the ability to express and to look for an effect of that expression. AR was also able to achieve, through a specific communication interaction, several perlocutionary effects. These are illustrated by the following conversation exchanges. First, when his daughter asked him: “How is your hand today? Does it hurt?” AR responds: “No”. His daughter, in surprise, asks for clarification: “It doesn’t hurt today”? AR, understanding her surprise element, then states: “No, nothing—you take good care of it, you are always working with it”. A few days later, AR’s occupational therapist tells his daughter that AR said to her that his hand “hurt a lot less now”. She then communicated to his daughter that she was surprised and very pleased it was healing so well now.

In both instances, AR’s illocutionary statements (“you take good care of it” and “it hurt a lot less now”) had the intended, positive perlocutionary effects upon the listeners. To his daughter, AR’s communication interaction expresses gratitude for her continual help with his hand pain. This exchange is meaningful for her as a surprising expression of thanks which encourages bonding and further caregiving efforts on his behalf. Similarly, AR’s occupational therapist is pleased by his illocutionary capacity to express his healing and gratified that her therapeutic efforts are reducing his pain.

5.6 Self-Depreciatory Humor & Use of Metaphors to Cope with Death

Kitazume [22] notes that self-depreciatory humor can also act as a tension release to cope with death which is a phenomenon that can cause great tension and anxiety. In the following conversation, AR's self-depreciatory humor about his old age actually opens up a discussion about the possibility of his impending death.

One day, AR's daughter asks him to see if he still knows: "How old are you?"

AR states that he doesn't know how old he is. Then he says, "125,000 years old" .

His daughter laughs then says, "You are 88 ½ years old."

AR responds: "That's pretty old---I feel old."

His daughter [now worried that this statement might mean that her father might be ready to die asks him with some concern]: "But you are not ready to go yet"?

AR responds: "No, not yet."

In this conversation exchange, AR's self-depreciatory humor might have initially had the illocutionary aim of using humor as a defense to protect him against a negative experience (being old) and as a way of grappling with possible fears his weakness arouses in him (memory loss leading him to forget his own age). One perlocutionary effect, however, of AR's communication was to arouse a *negative* (anxious) reaction in his daughter that her father might be communicating that he is dying or feeling ready to die. She, in turn, asks him for direct clarification of whether he was "ready to go yet?" to which he reassures her he is not. Thus, in this instance of pragmatic competence under targeted treatment, AR was able to use self-depreciatory humor in a multiple level exchange which incorporated cognitive and socio-interactive elements (to release tension, to protect against a negative experience and to reassure a daughter).

Lakoff & Johnson [57] argue that metaphors are used to conceptualize and make expressible relevant parts of our lives that are otherwise difficult to explain. Metaphors relating to the body such as "I'll just drift into sleep before your very eyes" or "It feels like I have come to a full stop" are often used to come to terms with difficult, physically disempowering experiences such as cancer or other late stage diseases [58].

On 12/4/18, as he was walking with his daughter in the rest home, AR employed a bodily-related metaphor: "I am tired. It seems like that is all I say. What a pain in the ass that is". In this instance, AR's use of a metaphor relating to his bodily state of being tired all the time ("what a pain in the ass that is") appears to function to try to cope with the frustration and perhaps even sadness of experiencing chronic fatigue of a late stage disease.⁵

5.7 Pragmatic Competence, Inferential Reasoning and Executive Functioning

The continued pragmatic capacity of this patient to have positive perlocutionary effects on listeners in multiple socio-interactive environments thus appears to reflect some important continued executive function capabilities and inferential reasoning; processes which require attention and the processing of multiple sources of information at the same time [21]. The two following communication exchanges demonstrate AR's relative lack of impairment in certain areas of executive-functioning.

⁵ Intriguingly, this speech utterance occurred fourteen days before AR's unanticipated fall, severe hip fracture and then undetected heart attack from which AR would ultimately die.

In this first conversational exchange, AR and his daughter have finished their walk in the rest home and have returned to his room. His daughter is having trouble with the door key to AR's rest home room, repeatedly trying to get it to work but not succeeding. AR correctly infers that she cannot open the door and asks in reference to the key: "Can't you get it inside"? His daughter: "No, I just can't push it in completely".

In a more detailed version of inferential reasoning, AR and his daughter are also walking back to his room and come up to a large automatic opening and closing door to the Alzheimer wing which is being held open by a staff member. AR has gone through this door many, many times on his daily walks. On this day, AR turns to his daughter and asks: "Can we go through"? His daughter responds: "Yes". Then AR, is able to remember, process and analyze contextual information simultaneously to warn her of possible impending danger when he commands her to: "Hurry up. It closes fast".

This latter statement strongly suggests the continued ability to process multiple channels of information, to have good inferential skills and to pay attention to the physical state of affairs around him. Specifically, it points to AR's capacity for inductive reasoning or to successfully reason and problem solve. This can be understood broadly, as an "executive function" under the attentional mechanism with the prefrontal cortex as the corresponding neurobiological substrate [59]. Similarly, the capacity to employ metaphors involves the capacity to abstract and to inhibit literal interpretation; both tasks associated with executive functions [31, 60]. Amanzio et al [59] found novel metaphor comprehension in AD was predicted by the "key search" task of the Behavioral Assessment of the Dysexecutive Syndrome (BADS) test which explores planning in the visual-spatial domain. The BADS "key search" task test has been found to be an accurate, general discriminator of executive functioning impairment versus non-impairment despite problems in further differentiating levels of executive impairment in MCI & AD patients [61]. There is no functional neuroimaging study of the neural correlates of the specific tasks. Nevertheless, fMRI studies of other visual-spatial planning task tests (Tower of London, Tower of Hanoi) show prefrontal cortex activity (the right ventrolateral and leftrostrolateral) which Amanzio et al [59] hypothesize as involving a similar neural network. The "key search" task of the BADS test reached a "medium" correlation with the "Rey Complex Figure", another executive function test measuring planning and organizational capacity [61, 62]. AR actually improved his score on the Rey Complex test by 9.2% (2014-2015) after 2 years on intranasal insulin, showed no deterioration in Digit Span and WORLD executive-functioning tests (2014-2015) [5]. He was also still able to spell WORLD backwards and count forward and backward by twos accurately at year five of targeted treatment (11/18) (Personal Communication 2019).

6. Pragmatic Competence under Treatment

This paper provided evidence of how extended use intra-nasal insulin treatment significantly augmented the use of humor, irony and sarcasm even in later stages of AD. This appears to support the hypothesis of enhanced neuronal activity in relevant brain areas associated with the capacity to detect, understand and respond to humor. In fact, studies have found the perfusion of the intra-nasal passage of insulin into the frontal lobes (prefrontal cortex areas such as ventral fronto-medial cortex), the temporo-occipito-parietal junction, the thalamus and the insular cortex)

[45, 63]. These brain areas correspond to the two main pathways of intra-nasal insulin, and, precisely, to the neural basis of humor processing [5, 64].⁶

Enhanced neuronal activity generated by extended intra-nasal insulin, in turn, appears to slow the progressive loss of pragmatic competence in AD in certain brain areas. We have shown the continued capacity to achieve illocutionary and perlocutionary functions in the domain-appropriate verbal responses of the expression of, and appropriate response to, humor. AR was able to play verbal games with caregivers, to use playful humor in group situations, to employ humor to assert autonomy and to assert humor to achieve sympathy. This continued pragmatic competence in the domain of humor is not an insignificant finding as AR achieved strong, positive perlocutionary responses by his listeners on multiple occasions, e.g. the expression by his main caregiver--“It sure beats his bitching” and the laughter expressed by nursing home residents and staff at AR’s various jokes. In another instance, one of the nurses at his facility exclaimed to his daughter: “He is so funny! I laugh at all the things he says”. This capacity directly reduced AR’s social isolation and enhanced opportunities for meaningful interactions [10].

AR was also able to exercise pragmatic competence in the expressive domain of empathy for others [6]. His illocutionary capacity to express to his daughter why he thought his hand was healing (“you take good care of it”) had the intended, positive perlocutionary effect on her of a surprising expression of thanks. Similarly, AR’s occupational therapist responded very positively to AR’s explanation that his hand “hurt a lot less now” and she conveyed to his daughter that she felt good that her treatment was working and that his pain was lessening. Such communication exchanges encouraged bonding and furthered caregiving efforts on his behalf. More generally, improved real communication with the patient as the result of targeted treatment has the strong potential to reduce caregiver stress [11, 12]. A patient’s continued pragmatic capacity involves expressing their own social, emotional and medical needs to others and relating to them emotionally in social conversation (to show and express affect, to be able to understand their own and other’s feelings). This can also increase the likelihood of being able to care for them with assistance successfully in their homes by family and caregivers for a longer period of time.

Another implication of our analysis is that despite changes in disease stage progression, targeted therapeutic treatment can permit the continued ability to employ non-literal language. AR was able to employ indirect illocutionary acts and certain pragmatic discourse markers

⁶ Studies of the intra-nasal passage of insulin (perfusion) through specific cortical region of the brain’s gray matter have shown increased perfusion in the following areas—the occipital cortex, the thalamus and the insular cortex [45, 63]. The neural basis of humor processing is assumed to engage a core network of cortical and subcortical structures precisely related to these regions. These include the temporo-occipito-parietal areas involved in detecting and resolving incongruity, i.e. mismatch between expected and presented stimuli and mesocorticolimbic dopaminergic system and the amygdala, which are both key structures for reward and salience [65]. The temporo-parietal junction incorporates information from the thalamus, among other systems. The thalamus is a relay from almost all sensory systems and relays the information to associated cortical areas. In addition, Clark and Warren [66] specifically note that in the cognitive neurology of humor processing, the insular cortex is engaged in an affective response to a joke. This perfusion into the occipital cortex, the thalamus and the insular context is hypothesized to follow the second main pathway of intra-nasal administration [5, 64]. Yet, comprehension of irony, sarcasm and self-depreciatory humor also relies on both cerebral hemispheres and ventral fronto-medial cortex, which is part of the prefrontal cortex [23, 67]. Metaphor appreciation has been found to be mainly the left-lateralized fronto-temporal network with some right hemisphere involvement [23]. The ventral fronto-medial cortex is the site of the first main pathway of intra-nasal insulin administration, i.e. the frontal lobes [5, 64].

("well"& "that's good") to express sarcasm in late-stage AD. Furthermore, AR was able to conceptualize, express and to try to cope with death-related anxiety by a complex of pragmatic functions: self-depreciatory humor ("I am 125,000 years old"), directly reassuring his daughter's anxiety ("But you are not ready to go yet"? "No"), employing bodily-related metaphors about chronic fatigue ("I am tired. It seems like that is all I say. What a pain in the ass that is").

This illocutionary capacity continued to occur *even though* AR also simultaneously demonstrated difficulties in word comprehension, common in early stage AD literal language deterioration [18, 19] and a manifestation of the most severe impairment of pragmatic inferential reasoning (an executive system impairment) [21, 68]. For example, one night, his daughter noted to AR, after listening to him repeatedly complaining about various aches and pains: "You are really crabby tonight" to which AR responded "What does "crabby" mean"? His daughter then explained: "Irritable, bad-tempered", then she asked: "Maybe you are tired"? AR then uttered the response. "Yes, I am tired." In this communication exchange, AR was still able to satisfy felicity conditions of the performative utterance despite some significant deterioration in word comprehension. He expressed sincerity (intention) and used words appropriate for the circumstances ("Yes, I am tired") appropriate to the context which then had the intended (perlocutionary) effect on his daughter (agreement with her). This suggests that improvements in pragmatic competence can occur with extended intra-nasal insulin treatment even if other linguistic and cognitive capacities (e.g., some aspects of inferential reasoning, word finding, word interpretation) deteriorate.⁷

Preservation of pragmatic functions and pragmatic inference generation under targeted treatment also appears strongly associated with the slowing of the pronounced rates of executive function in terms of attention span and visuo-spatial deterioration [5], typically those cognitive dimensions in AD that decline annually most rapidly [50]. This is consistent with the frontal lobes' pathway of intra-nasal insulin, as the left lobe is a key site for pragmatics and the same region functions for motivation, working memory and executive functions [69]. The inhibitory abilities [70], the attentional [71] and the visuospatial functions [72] are those executive-functions specifically compromised from early stages in AD primarily due to degeneration of the prefrontal cortex [73]. Any slowing of the development of akinetic mutism, associated with poor fluency scores, increased mortality and frontal subcortical impairment in AD [74] reduces suffering. Future work is required to determine the specific, additional functional impacts of nose-to-brain pathways of intra-nasal insulin transport and aspects of improved pragmatic competence in MCI & AD.

⁷ For example, AR deteriorated by year five and a half after AD diagnoses and year five of intra-nasal insulin treatment in orientation to place, time, and had confusion about family members and their correct roles. Nevertheless, even at that point (6/18) he was still always able to ask valid questions of events transpiring around him, e.g. "Who is that person?", "What are they doing?", "What did she/he want"? "Why would he do that"?, "What city are we living in?", "What is the name of this place"? "What is that?". AR's continued ability to ask such questions can also be understood as part of pragmatic competence as it demonstrates the use of language in appropriate social context even if his cognitive capacity to understand such situations and his short-term memory was significantly compromised. Moreover, AR was still able to issue commands such as "careful" or "don't knock me over" when being assisted to get up from a chair. Finally, AR was also able to focus his attention span by looking at books in the evening and "reading" them for 30 minutes or more at year five after AD diagnosis even as more word loss occurred and pronunciation deteriorated.

7. Conclusion

The focus on pragmatic competence, specifically on humor and illocutionary and perlocutionary functions, finds that extended intra-nasal insulin treatment significantly augments the use of humor, irony and sarcasm even in later stages of AD. Our model considers pragmatic units not only as utterance elements, but also as units incorporating cognitive and socio-interactive dimensions, which are essential in the determination of the success of the perlocutionary and illocutionary functions associated to speech acts. This model of pragmatic competence under targeted treatment supports the hypothesis of enhanced neuronal activity in relevant brain areas associated with the capacity to detect, understand and respond to humor. Treatment-mediated improvements in neuronal activity in certain areas can bring moderate to significant improvement to communication exchanges thereby reducing the AD patient's social and communicative isolation and lessening caregiver stress. In sum, our research supports the growing body of literature on intra-nasal insulin treatment and its positive impact in the improvement of cognitive functions.

Additional Materials

The additional materials are uploaded at the page of this paper.

Author Contributions

Dr. Schatz's contribution to this paper is in the area of Alzheimer's disease. Dr. González-Rivera contributes in the area of linguistics (pragmatics).

Competing Interests

The authors have declared that no competing interests exist.

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