

Pragmatic Competence and Intra-nasal Insulin in Advanced Alzheimer's Disease

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ABSTRACT

This article examines the recovery of pragmatic competence in a moderately-severe Alzheimer's (AD) patient after 12 weeks of treatment with intra-nasal insulin treatment (INI). The patient rapidly recovered the ability to use the language of bodily awareness, emotional self-awareness and empathy. She also began to pay attention and to re-engage in pleasurable social interaction which reduced family and caregivers stress. The communicative shift from severe aphasia at base line to improved pragmatic competence strongly suggests that INI has a rapid, positive effect even at later stages of AD disease progression in areas of the brain centrally associated with subjective interceptive awareness (the insular cortex, thalamus) and executive functioning skills.

Keywords: Pragmatic competence, Alzheimer's Disease, Executive functioning, Language ability

INTRODUCTION

This article examines the rapid recovery of pragmatic functioning¹ of a moderately severe AD patient after 12 weeks of treatment with intra-nasal insulin treatment (INI). Previous studies of cognition and pragmatic competence and intra-nasal insulin have examined its effects in MCI and early to moderate AD patients, finding improvements in cognition and verbal working memory and in three main domain-appropriate verbal responses (self-expression of medical, social and emotional needs, humor and empathy) [2-7]. Improved illocutionary force and perlocutionary effects in these three pragmatic domains encourage bonding with caregivers and enhance the likelihood the patient will be effectively cared for in their home [8]. This is the first time INI treatment has been assessed for pragmatic competence in the later stages of AD.

Section I of this article (Language Abilities in Moderate to Late Stage AD, Patient History & The Promise of INI Treatment and Pragmatic Competence in AD) examines loss of pragmatic competence in this patient and increased caregiver stress because of the patient's inability to communicate. It also focuses on the dynamics of language ability and aphasia in moderate and late stage AD as well as

the ability of INI therapy to improve pragmatic competence in several verbal domains.

Section II ("Coming Out of the Fog" & "Rising Bodily Awareness & Self-Expression") shows how the patient initiates a return of illocutionary effect (or the capacity to communicate her feelings and to express sincerity) under initial treatment. This, in turn, causes an increased perlocutionary effect as family and caregivers respond to the patient's improved illocutionary capacities. Particularly in the areas of bodily self-awareness and bodily needs with laughter, pleasure and improved emotional bonding are notably improved. Improved communication reduces social isolation of the patient and eases caregiver stress. Section III ("Episodic Memory Retrieval, Rising Executive-Function Attentional Skills, Sarcasm, Metathesis & Increasing Illocutionary Sophistication") provides examples of how treatment-mediated enhanced pragmatic capacities provide opportunities for meaningful communication with the patient; thereby further reducing the likelihood of social withdrawal, loss of confidence and depression.

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¹Our model [1] considers pragmatic units as both linguistic 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.

Section IV (“Empathy & Self-Awareness”)—demonstrates the expression of higher-level social emotions, including empathy, love, self-depreciatory humor and the patient’s increasing “give and take” in conversational exchanges. Section V- (“Pragmatic Competence under Treatment”) draws several neuroanatomical conclusions with respect to the INI treatment-mediated return of the language of bodily self-awareness, episodic memory and empathy even in the later stages of AD.

SECTION 1

Language Abilities in Moderate to Late Stage AD

Typically, language impairment as an element of cognitive loss in AD is often restricted conceptually to anomia (aphasia) [9]. The literature on impaired linguistic and neuropsychological features of the most common aphasia in AD (lvPPA) syndrome² discusses non-fluent spontaneous speech, phonemic errors, impaired episodic memory and slower speech [13]. Although patients with lvPPA are still able to produce speech, their speech rate may be significantly slowed due to word retrieval difficulty, and, over time, they may experience the inability to retain lengthy information, causing difficulty understanding complex verbal information. [14,15] AD (lvPPA) patients also display additional cognitive and behavioral features which include irritability, anxiety and agitation [16]. Apathy is also a consistent feature in AD (lvPPA) [17].

There are few descriptions of the actual language skills of persons in late-stage AD [18]. In the 1980s, studies of spontaneous verbal output found that by the late disease stage (stage 7 on the Global Deterioration Scale (FAST) “all verbal abilities are lost” and “frequently there is no speech at all—only grunting” [19]. Speech and language in AD patients are not mentioned in the FAST until stage 7a, when they are characterized as having the “ability to speak limited to one to five words” [20]. By stage 7b, they are characterized as having “all intelligible vocabulary lost” [20,18]. Pragmatic competence has thus decayed to the point where meaningful communication with caregivers is absent or so impaired that “(social) isolation, depression and decreased quality of life” for the AD patient are often the result [21-23].

Recent studies of language output in moderately-severe to late stage AD shed a new light on the issue. Studies have begun to incorporate more pragmatic elements including the social context of communicative exchanges, as well as

cognitive elements (specific questions). As such, scholars have expressed “surprise” that many of the individuals³ who were not bedridden produced “intelligible, meaningful sentences” in response to communication probes [18]. The following are examples of patient answers given to stimulus questions such as “Where would you like to go on a trip?” and “What is your favorite food?” by the moderately severe: “Right now I think I’d like to see Hawaii”; “Fruit of all kind is all right with me, I love fruit”; “I don’t think I ought to go anywhere cause I’m in bad shape”; “Depends on what you have in your mind”; “I’d go away from here”; “I eat quite a bit”; “I doubt if I’d even go on a trip.” Examples of utterances produced by individuals rated as severe include: “Not interested in that”; “Wouldn’t even think of that”; “I’d have to think a long time about that”; “I eat a lot of things now”; “I don’t know”; “Can’t tell”. Even the majority of bedridden patients produced words [18].

Similarly, Moos [24] found that in open ended interviews in naturalistic setting with three moderately severe to severe patients, some did occasionally employ such pragmatic elements as humor, irony and sarcasm. One patient with middle stage AD “Sigrid” whose speech was normally imprecise, ambiguous and with pronounced word-finding difficulties, was able to employ direct sarcasm to her caregiver. The caregiver was pressing her to get up out of bed but then got summoned to another room. Sigrid then said with an angry and biting tone: (go) “so you can go and do what you are good at” [25]. In another instance while listening to music, Sigrid was able to tell the researcher with “unusual clarity” and “ironic understatement” that she knew the song’s author [25]. Typically, the capacity to detect, understand and respond to sarcasm, figurative utterances, deteriorates significantly in the progression of AD [26].

In general then, the literature on language capacities in moderately severe to late stage AD reports significant pragmatic impairment, progressive loss of communication abilities and social withdrawal occurring from loss of linguistic function [27,28]. Exceptions to the rule of severe language deterioration (intelligible, meaningful answers to communication probes, the very occasional use of the communicative strategies of humor, irony and sarcasm in naturalistic conversations with care-givers) imply retained pragmatic capacity [18,25]. Explanations for this limited pragmatic capacity are non-specific and refer exclusively to social elements (e.g. power dynamics or in response to an unbearable situation as when caregivers were intruding on their privacy and autonomy) [25]. This explanation, however, still leaves open the question of if and how improvements in pragmatic competence in moderately severe to late stage AD could be achieved.

Patient history

KG is a 76-year-old divorced woman with two sons. She was married for 15 years and worked as a paraprofessional

²Primary progressive aphasia (PPA) is a syndrome which slowly damages the parts of the brain that control speech and language. People with PPA typically have difficulty speaking, naming objects or understanding conversations. One form of PPA is called the logopenic variant (lvPPA). lvPPA is the most common aphasic phenotype in AD (77%) [10-12]. In lvPPA there is a large build-up of proteins called amyloid and tau within brain cells. These are the same proteins that build up in Alzheimer’s disease. “As more and more proteins form in brain cells, the cells lose their ability to function and eventually die, causing the affected parts of the brain to shrink [13]”.

dental worker. She had a life-long struggle with depression. At AD diagnosis in 2016, the patient was living alone, losing weight because she had stopped eating and was facing increasing difficulties in self-care. Her daily medications at baseline included Lexapro, Memantine, Aricept, Megestrol, Aspirin, Vitamin B-12, Omeprazole, Lipitor and Norvasc.

In early 2020, KG's neurologists diagnosed her as "very depressed" and recommended more intensive treatment for her AD and more testing. According to KG's brother, she rebelled against this doctor's advice and became combative [29]. Shortly thereafter, her brother noted that when he began to care for her in his home, her cognition had deteriorated significantly since he had seen her 4 months previously. By February 2020, he concurred with her doctor that KG's mood was very depressed and that her disease progression had worsened. By the FLCI (Functional Linguistic Communication Inventory), KG would be rated as "moderately severe" [30]³.

Caregiver despair

Interviews with KG's brother clearly illustrate the caregiver stress and despair that emerges when a loved one with AD is unable to communicate. At baseline, KG was apathetic and almost totally aphasiac. She required 24/7 care and, after caring for his sister with his wife and a paid caregiver for several months, her brother spoke specifically of how difficult it was not to receive a response to talking to his sister:

"She sleeps all day and it takes two people to get her up and to take her to the table to feed her. She often doesn't want to eat so it is a battle to feed her. She is constantly incontinent; we are constantly changing her diapers. She has no control over herself and she doesn't know what she is doing. At what stage are we at in the disease process where nothing helps? We can keep her in bed, time will pass.... I just don't know how to reach her. Four months ago, she was not nearly as bad as now, she has declined a lot".

In Schatz and Rivera [8], we hypothesized that such psychodynamic principles as flattening of affect and social and linguistic withdrawal (often associated with the irritability and upset that characterize AD [lvPPA]) could be understood as the by-products of loss of illocutionary and perlocutionary functions. As patients become increasingly unable to express themselves (loss of illocutionary force), withdrawal and frustration are evident in the listener as there is a lack of intended outcome (perlocutionary effect). The following description of KG's daily routine from her brother reveals how the flattening of affect, lack of words and irritability directly impacts her caregivers.

"Our daily routine is that (my wife) showers her. Her bedroom reeks of urine, my wife has to hold her although

she can move her legs and walk, she is a fall risk. She combs her hair, we have to wash all the clothing, shift the bed, try and feed her breakfast. Then we take her to the TV where she sits and likes "I Love Lucy" and then we need to try to keep her awake. Somehow, she always goes to sleep. We ask her: 'What do you want to do?' She says: 'Go to bed, I love to sleep.' After a while, we put her back to bed...my wife and I trade off, washing clothes, we cannot leave her alone. I try to take her out into the fresh air but she doesn't talk or say anything like "This is nice". She is not articulate; they say it is late stage. 'What can I do for her?' 'I don't know'...spend time with her. She does know me. I ask her: 'Did you eat your breakfast?' 'No', she says even though she did. I ask her: 'Did you watch TV?' 'No', she says even though she did. She has no short-term memory. I feel like it is really hard to read somebody all the time, especially my sister. I do because my wife has to go back to work."

KG's lack of words then represents a perlocutionary and illocutionary breakdown-KG's brother feels helpless to reach her in the sense that he has no measure of his efforts, no accurate verbal responses. Tappen et al (2002) note that the progressive loss of ability to communicate is "one of the most tragic symptoms of Alzheimer's Disease". Adverse consequences for the older individual and their loved one often result from this loss of language capacity. The AD patient often suffers from increasing "isolation, depression, disturbed behavior, and decreased quality of life" [21]. Caregiver stress is "endemic" due to the low levels of communication with the patient [23]. The AD patient's reduced capacity for empathy can also have significant negative consequences on caregivers and marital relationships especially in later disease stages [32].

Caregiver stress and the real difficulties that arise when caring for moderate and late stage AD patients in their own homes is clearly illustrated in this final conversational exchange. In it, the patient's brother describes his conversations with his wife about his sisters' future care.

"We have philosophical discussions. Should she be in a room and care (nursing home) but she has no income. We would have to borrow money. We go back and forth about where she would be better off, at home here with us or in a facility.... I don't mean to wail. This is a game changer. It is such a hard thing to see her like this. 'Oh my God—This is what happens to people'".

The promise of INI treatment and pragmatic competence

Previous studies of the capacity of INI therapy to improve pragmatic competence were analyzed using a model of cognitive decline and improvement that included pragmatic units [8]. Specifically, this model incorporated pragmatic units as specific speech utterances focused on several verbal

³[30] defined those who were bladder-incontinent but not bedridden as "moderately severe".

domains in MCI and mild to moderate AD [6]⁴. Using conception of performatives [1], these utterances can be understood as speech acts which are considered to “do something”. In other words, to perform acts of different sorts: thank, name, apologize, etc. Such speech acts contrast with “constatives” or language use whose function is to describe states of affairs.

This model examined three acts related to an utterance. These included the “locutionary act” or act of saying something meaningful, the “illocutionary act” (the act performed in saying in something) and the “perlocutionary act” or effect that emerges as the consequence of saying something. Improved illocutionary capacity refers also 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 through 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” [8].

Performative 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 circumstances⁵.

After treatment using intra-nasal insulin in persons with MCI and early to moderate AD, it was 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 conversational exchanges. This improved their illocutionary capacity, and in turn, had direct, positive perlocutionary effects on their listeners (caregivers, spouses, friends, doctors) who expressed pleasure that the patients were so “present”, “fluent in language”, “happier”, “less grumpy” and had a “better quality of life” [3,8]. This model of pragmatic competence then considers pragmatic units not only as utterance elements, but also as units incorporating cognitive and socio-interactive dimensions, which are essential in determining the success of the perlocutionary and illocutionary functions associated to speech acts.

In certain studies [5], this line of research was further developed in an extended INI use (five years +) patient with moderate AD (“AR”). It was shown how extended INI treatment significantly augmented AR’s use of illocutionary

and perlocutionary abilities in the areas of humor, irony and sarcasm. This patient’s continued illocutionary capacities to employ self-depreciatory humor, sarcasm, verbal games, and even metaphors had significant perlocutionary effects on caregivers, family and doctors, arousing sympathy, laughter and pleasure at AR’s continued pragmatic competence. As one of his nurses spontaneously proclaimed--“He is so funny”! I laugh at all the things he says” [5].

This illocutionary capacity continued to occur even though AR simultaneously demonstrated deterioration in other aspects of linguistic and cognitive capacities (short and long-term memory, difficulties in word comprehension, word finding, some aspects of inferential reasoning). INI treatment-mediated improvements in pragmatic competence suggest that cognitive impairment should be understood not just as processes and domains related mostly to memory (short/long term recall) but also to include perception, language, self-awareness and awareness of others [5,8].

With respect to moderately severe to severe AD, INI still has the potential capacity to reach areas of the brain centrally related to near complete aphasia.⁶ INI has been shown to increase cerebral blood flow, increase perfusion in grey matter and reduce decreases in cerebral glucose metabolic rate, thus curbing the development and progression of AD.

Yet, INI treatment and pragmatic competence has not been systematically researched in later AD disease stages. Previous published studies of MCI and early AD patients using short-term intra-nasal insulin (4 months or less) showed significantly less decline in cognition and working memory when compared to the placebo group (as measured by standard neuropsychiatric tests in MCI and early AD, Voice Onset Time, Delayed Story Recall Score) [2]. Caregivers also observed INI treatment-mediated improvements on the Dementia Rating Severity Scale and ADCS-ADL scale as compared to the placebo group [35, 2, 3]. One INI MCI patient was administered a series of pre- and post-therapy neuropsychological tests, including visuo-spatial skills, visual spatial ability, visual working memory and executive-functioning [5]. Eight months after beginning intra-nasal insulin, his neurologist stated that: “There was about a two-year reversal of cognitive impairment while receiving intranasal insulin, going from mild dementia to

⁴The promise of intra-nasal insulin as a therapy to preserve language, cognition and memory for AD sufferers, their caregivers and families has a history since 1989. For a complete review of the safety of INI, see: [33, 34].

⁵This refers to “felicity conditions” or those conditions which have to be satisfied in order for a performative utterance to be satisfactory. For a more extended linguistic discussion on this point, see [8].

⁶The pathway of INI traverses a core network of cortical and subcortical structures relating to the insular cortex (subjective awareness of inner body feelings and emotionality, engagement in an effective response to a joke), the neural basis of humor processing (temporo-occipito-parietal areas, the thalamus, the right parahippocampal gyrus) and the prefrontal-hippocampal loop that enables encoding and retrieval of declarative memory [36-38, 29]. Logopenic progressive aphasia is caused by damage to segregated brain regions [12]. Brain imaging revealed atrophies in left posterior superior temporal, inferior parietal lobe (thinning causing difficulties in naming), medial temporal, posterior cingulate, anterior temporal and frontal cortical regions [14, 15, 10, 11]. The thalamus mediates from the superior temporal cortex and posterior parietal cortex (Jones 2007) and INI has been shown to increase perfusion into grey matter in the thalamus [39].

mild cognitive impairment [6]". Thus, INI's ability to reach the insular cortex, thalamus, and prefrontal-hippocampal loop make AD a bit less of a "devastating disease" [40]. It still holds this promise of pragmatic competence improvement even in later AD stages.

This article hypothesizes that INI treatment has the potential to enhance pragmatic capacity in moderate to late stage AD. Enhanced neuronal activity, especially in the insular cortex, is particularly promising for enhanced pragmatic competence as it can augment subjective awareness of bodily and emotional feelings and socially to properly engage in an effective response to a joke. For example, patient AR began INI treatment at early to moderate AD diagnosis (6/13, MMSE 24) and had begun to show marked signs of irritability, social and linguistic withdrawal and lack of empathy by 12/12 [8]. Yet, his Global Deterioration Rating (GDS) rating after two years on INI treatment was very high (2015:2/30) and his family did not see signs of depression post-treatment.

METHODS

Section II

Rising pragmatic competence post-INI treatment

Coming out of the fog

In this section, it is shown how the patient initiates a return of illocutionary effect (the capacity to communicate feeling) and ability to express sincerity under initial INI treatment. Previous research direct our attention to the importance of statements of MCI & AD patients uttered early on in their treatment as subjective descriptions of their previous mental state. One man (IL) said that the intra-nasal insulin treatment "was good because it made my head feel much clearer [8]". Another man "AR" put his head in his hands and spontaneously stated to his daughter after two intra-nasal treatments, "Oh, my head has been hurting so bad. It is like I have been in a fog." AR's girlfriend also immediately noticed his improved mood, less irritability and a return of illocutionary and perlocutionary capacity after a week of his INI treatment began, stating: "You are happier now, less grumpy" [8].

In KG's case, her brother had that she would be starting the intra-nasal insulin treatment and explained how it was administered. Consistent with KG's limited, pre-treatment verbality, she was silent and did not respond to this explanation. On day #2 of the treatment, however, the following conversation took place which illustrates the return of treatment-mediated illocutionary and perlocutionary functions.

Patient KG says spontaneously: "Can I help you with what you are doing?"

Brother: "She never said that before. We looked at each other and said: 'She is speaking'. It can't be happening

now'. And then the caregiver said: 'She is talking like crazy'.

Researcher [introjects]: "Is this all new"?

Brother: "This is all new. She was never so chatty. So, then we all looked at each other and said— 'Something is working' so we tried to verify it. And then today after the third day of treatment, she said: 'I like this' and started to laugh, laugh, laugh, laugh and we all laughed."

This vignette illustrates a partial return of the illocutionary function; that is to say, the capacity of an AD patient to be able to communicate her feelings and to use words appropriately to express sincerity (intention). This also represents the emergence of perlocutionary effects related to illocutionary capacity: the ability to express and look for an effect of that expression. KG's use of words correctly ("I like this", "Can I help you with what you are doing?") and her new found flow of words ("chatty") had the effect of validating her brother, sister-in-law's and caregiver's feelings that something about the treatment was working.

Rising bodily awareness & self-expression

Self-awareness of distinct emotions and bodily feelings such as pain, temperature, itch, visceral sensations, hunger, thirst, taste, and even sensual touch are related to homeostatic mechanisms in the brainstem and hypothalamus. In humans, individual subjective awareness of these inner body feelings and emotions (the "material" me, how you feel, the physical plane of existence) is mediated by the thalamo-cortical extension of these pathways to the insular cortex and specifically to the rAI (right anterior insular cortex) [36]. Intra-nasal insulin increases cerebral blood flow and perfusion through gray matter in both the thalamus and the insular cortex [39,37].

KG began to describe her bodily sensations during the first week of the INI treatment. These illocutionary speech acts express her physical condition, something she had not done for at least 4-6 months prior to treatment. On the second day of treatment she said: "I have poops" and asked to go to the bathroom for the first time. On the third treatment day, she stated she "did not want to get out of bed", something she had not previously articulated⁷. On the eighth day of

⁷With this heightened self-awareness and pragmatic abilities also came newly expressed anxiety. The patient woke up on the third night of the treatment and said "I was afraid" "I thought you left me" and several times she repeated that she was "scared". Her family reassured her at that moment that she was not alone and that she was in a safe place. They put on music and she started mouthing the words of the song and then asked again about her location. After calming down a bit, she started repeating again: "I'm lost, I'm lost, I'm lost" and again they reassured her that she was living with them. Her sister-in-law wrote in her notes on the patient that it was very unusual for "KG to be so verbal, rather than in the usual daze. I can't remember last when she talked about her emotions this way".

treatment, KG asked her caregiver to give her small hand balls to help declaw her hands.

At one month of treatment, the patient's brother also summed up her progress in terms of his sisters' rising bodily self-awareness. He noted: "She [now] says things that she cannot do. So, she expresses herself. When she cannot do something, she knows it. When she is afraid, she says it. So, it is just more like her old self in a way where she would comment on things; sometimes not happy with something. And, she would say so, like "I'm cold". Then her brother turns to the patient and asks: "Are you cold?" "Are you cold?"

Patient: "Not right now."

Brother: "Not right now, she said, not right now. That means she will be cold later".

As Schatz and Rivera [8] argue, a patient's continued pragmatic capacity to express their own social, emotional and medical needs to others may also increase their likelihood of successful in-home care by less family and caregivers. The emergence of these perlocutionary effects in response to increased patient illocutionary capacities, in turn, reduce the social isolation of the AD patient and encourage further bonding opportunities.

Section III

Episodic memory retrieval

Krug et al (2010) that in women, in contrast to men, intranasal insulin acutely enhances the function of the prefrontal-hippocampal loop that enables encoding and retrieval of declarative memory [41]. INI enhances the performance of prefrontal cortex dependent working memory tasks, recall, and recognition tests. When involving the right frontal cortical regions, this includes the retrieval of information from episodic memory when patients are exposed to words, faces, and drawings of objects [42]. Left frontal activation signals the involvement of the left-frontal cortical regions in the encoding of novel information into semantic episodic memory with respect to verbal or verbalizable materials.

The patient also began to retrieve information from episodic memory drawn from visual recognition of faces. For example, after 10 days of treatment, the patient was looking at a home movie of herself dancing at her relatives' wedding and declared, spontaneously: "I remember that!". The patient at one month of treatment was able, similarly, to recognize her brother's friend in an old (25 years) home video after about 5 minutes of concentrated visual focus on the film. After failing to recognize herself, her mother and her sister, she stated: "That's my brother in the front!". This visually based episodic memory retrieval and illocutionary pronouncement, in turn, caused a positive perlocutionary effect on her sister-in-law who declared with pleasure: "That right!".

Another example of treatment-mediated episodic memory involves semantic retrieval and is illustrated by the following vignette. The patient is being asked by her sister-in-law for details about the "I Love Lucy Show" that they like to watch together.

Sister-in-law: "What is the name of the show you like to watch with me all the time?" "I" ... "Love" (pauses)

Patient: "Lucy"

Sister-in-law: Smiling, laughing, "Yes" (with emphasis)

Sister-in-law: "And, uh... what is Lucy's husband's name?"

Patient: Silence, she continues eating.

Sister-in-law: "And who is Lucy's friend?", and she gives her something to drink.

Patient: "I don't remember"

Sister-in-law: "And her husband plays what instrument?"

Patient: Silent

Sister-in-law: "Sometimes we watch movies, and a movie star looks like you. Which movie star looks like you?"

Brother (intjects): "Who is your favorite movie star?"

Patient: "Elizabeth Taylor"

Sister-in-law: Very pleased, smiling: "Yes"!!

Patient: Smiling

Sister-in-law: "And you look a lot like her, huh"? Laughing, very, very pleased (leans in toward patient).

These treatment-mediated memory retrievals further illustrate improved illocutionary and perlocutionary capacities. The pleasure derived by KG's family stems from her new-found ability to accurately articulate her memories of self and family recognition. Their laughter, smiles and emphatic responses (yes, that's right!) represent strong, positive perlocutionary responses to KG's improved illocutionary abilities to express her memories. The following exchange at one month of treatment further illustrates improved perlocutionary functioning.

Visiting Handyman (VH): "KG, what is your last name?"

Patient: "James".

Brother (surprised, pleased): "James-That is you son's name".

Sister-in-law: "And who is your other son?" "Who is the older son?"

Patient: "Jonah".

Brother [Happy]: "Jonah! Ok. Good for you!".

Sister-in-law: "And which one is taller? Which one is bigger—James or Jonah?"

Patient: "James".

Brother and sister-in-law both exclaim: "Yes, he is". (Smiling, laughing). Brother: "You got it right!"

(Patient has expression of trying to pay attention. Partially smiling, more focused).

Brother: "How are you feeling today?"

Patient (turns her head toward her brother): "Good, I guess".

Brother: "Alright, and how do you feel everyday—do you feel you are getting tired or feeling tired?"

Patient: "A little".

Brother: "A little tired?"

Patient: "A little".

Brother: "Do you feel good?"

Patient: "Yep, I feel good."

Brother: "Excellent".

In this instance, KG's accuracy in identifying her son (even though she mistook his name for her last own name) has a positive effect on her family ("Ok, good for you!", "You got it right!", "Excellent!"). KG is also able to produce nuanced answers to the question of how she was feeling that day ("Good, I guess", "A little tired"). This implies some doubt, self-awareness of that doubt and improved illocutionary capacity to verbalize the doubt.

It is important to contrast these new performative utterances in comparison with the patient's pre-treatment aphasia where she would utter largely inaccurate, monosyllabic responses. KG's brother noted his sister's increasing pragmatic capacities, stating in a video interview: "This is KG-she is really improving because she is responding more to questions, she is more accurate in her responses (emphasis) She is also, for the first time in a long time, giving us complete sentences. The other day she said to me, she said:

"You sure are eating a lot. I want to eat a lot like you too. Where can I get some food?"

Her brother noted, "So that was amazing that she said 3 sentences in a row."

Then he turns to her and asks: "Remember that?"

Patient: "Yea"

Brother: "When I dance like this"—(brother proceeds to jump up and down in a comical way, laughing).

Patient: smiles, looks happier.

This treatment-mediated increased pragmatic capacity of his sister to construct longer, more complex sentences contrasts with speech characteristics of mid-to-late stage AD. Typically, linguistic behavior at this stage is characterized

by multiple semantic and lexical speech features such as stutters, self-corrections, and empty pauses [31]. Social isolation from other speakers is the ultimate effect of this loss of linguistic function as a negative spiral downward occurs which is interactive (patient and caregivers) and encompasses significant social and pragmatic effects. Wray (2015) writes that as language becomes compromised by "short term memory loss, distortions in lost contextual information", AD patients in the early to mid-stages will try to rescue the situation, compensate or cover up their problems or avoid interaction all together [22]. By KG's late moderate-late stage AD, her pre-treatment speech reflected her progressive aphasia to the point of mutism, as was noted above in section I.

In contrast, under treatment, KG was able to express confidence about remembering the visiting handyman was even though he had been away for 3 days. The following vignette shows the patient asserting herself in her power when the handyman is surprised by her memory capacity.

Visiting Handyman (VH) (who had been out for 3 days) enters the room and says to the patient: "How are you?"

Patient: "Good. Nice to see you".

VH (looks pleased and surprised): "Oh, you remember me?"

Patient: "Of course" (with emphasis).

This interaction provided another opportunity for meaningful communication with the patient. In terms of pragmatic competence, INI further reduces the cycle of social withdrawal, loss of confidence, depression and altered power relationships characteristic of the loss of pragmatic competence in AD [8,22].

Rising executive-function attentional skills & eased caregiver stress

Executive functioning is, by definition, inextricably associated with the various cognitive, linguistic and sensorimotor elements in the intrapersonal domain over which it exercises control [7]. Executive function and inference require simultaneous attention and the processing of multiple sources of information in parallel. Paying attention in terms of pragmatic competence involves the capacity to remember one's everyday experience and keep track of their own narrative and be able to reply to questions with words rather than gestures. Boyd et al (2013) persons with dementia are often not able to retrieve and produce a specific topic from memory and/or maintain personal agency in complex conversational exchanges [43].

In contrast, KG was watching a TV show that her brother has put on inadvertently in Spanish. Suddenly she said: "I don't understand what they are saying". This had the immediate perlocutionary effect on her brother, who noted with surprise and pleasure: "I didn't even know she was paying attention." A few days later, the patient was watching

the movie “Anne of Green Gables”, and was markedly more alert, according to her caregivers and made appropriate comments which pleased them. Increased attention span and a lessening of social withdrawal has been previously found in patients with Phelan-McDermid Syndrome after intranasal insulin [44,45].⁸

The patient also became increasingly aware of and able to express her own self-limitations when asked to perform a task. For example, the patient’s brother was assisting her to eat breakfast one morning and was feeding her eggs then asked her: “You want to try eating yourself? Try eating this banana yourself. Try feeding yourself.” The patient focused visually on the banana and tried to take a hold of it but her hand was so clawed that she could not grasp it and said: “I can’t do it”. On another occasion, the patient was asked if she knew what kind of food she was eating, and she answered “No”.

The patient’s caregivers also report decreased burden and stress in caring for her. For example, her caregiver stated the following after the first month of treatment in a video interview: “KG is different in her eyes, I think (she touches her heart), and, um, when I go to get her up in the morning or when I get here, she’s willing to get up, you know, before she would want to stay in bed a lot, and, they are very small (pinched finger gesture) but I think they are significant little things, you know, she talks more....She says her prayers at night, and she is more aware of what is happening; what’s going on”.

After 6 weeks of treatment, the patient brother stated his sister had “really improved”, and “she is no longer in a daze. She now has more moments of lucidity, she is more alert, awake longer. It is now hit and miss-if I say: ‘How do you feel now’, she might mumble but then later she will be watching TV and laugh. Her eyes are more focused, not dreary. She is paying attention”.

Sarcasm, Metathesis & Increasing Illocutionary Sophistication

Sarcasm has commonly been understood as a severe form of irony often intended to insult or wound, i.e. associated with negative psychological effects. However, 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 [46]. In the following self-commentary, the patient expresses self-depreciatory humor. While listening to music on day #6 of treatment, a song called “When I fall in love”, the patient

commented, in a sarcastic tone: “That is not going to happen”. Similarly, when a second song entitled “Ain’t we got fun” came on, the patient said: “I am not having fun”.

In the first of these verbal utterances, the patient is using self-depreciatory humor (“That is not going to happen”) to grapple with her own knowledge that she is too old or ill to fall in love. This implies the cognitive capacity to recognize that one is old and very likely past the age of romance. The second response (“I am not having fun”) is more of an indirect complaint or the expression of unhappiness with her current circumstances. As a pragmatic speech act, an indirect complaint represents the expression of dissatisfaction or annoyance to a listener about oneself (“I am not having fun”) but does not hold the listener responsible for a perceived offence [47]. Both of these unusual verbal utterances (for this patient) elicited the response (perlocutionary effect) on the caregiver of “interesting”!

In another conversation exchange on day #10 of treatment, the patient responds to a question about her location which has the perlocutionary effect of a joke.

Brother: “Hi KG, how are you today?”

Patient: “I am doing pretty good”.

Brother: “Do you feel better?”

Patient: “Yea.”

Brother: “Where are you?”

Patient: “Right here”

Brother: (laughter) “That’s a good answer”.

In this instance, the patient appears to be compensating for her lack of knowledge (memory) regarding her orientation by making a joke (“I am right here”, although she may not really know where she is in terms of orientation).⁹ The patient is also beginning to use more words in a sentence response (“I am doing pretty good” rather than just “good”).

This vignette suggests that the patient is able to verbalize a response to the question of her orientation rather than just remain mute, which was her pre-treatment response. The illocutionary force of the speech act may simply be “declarative” in a basic, concrete sense (“I am right here”). In this instance, irrespective of whether the patient’s intention was to make a deflective joke, or to express simply concreteness, the immediate perlocutionary effect on the listener was laughter. Her brother’s positive response was: “That is a good answer!”

⁸The neuroanatomical mechanisms of INI treatment’s improvements in executive function are not well understood but [44] as Schmidt et al (2009) and Kolvezon et al (2014) hypothesize enhanced neuronal function by increasing CNS glucose uptake and enhancing synaptic plasticity via glutamatergic receptors in Phelan-McDermid Syndrome [45].

⁹On that same INI treatment night of #3 (see footnote 7) when KG awoke with abandonment anxiety, her family has her listen to some music to calm her down. KG started mouthing the words to the song and then she asked upon her location. Her family told her she had moved from her condo and was living with them. This was the first time KG had talked about her location in several weeks. However, she kept going back to the anxious distress, saying: “I kept calling you. I was calling your name”.

The patient again demonstrates improved illocutionary capacity in a spontaneous speech utterance that is clearly a metathesis¹⁰.

VH says to the household in which the patient lives after working all day:

"I am going home now. I am tired".

Patient spontaneously asserts:

"Are you tired or re-tired (with emphasis)?"

VH then laughs, taking her utterance as a joke because he works very long hours in general, is also of retirement age and has been frequently told by people he is a "work alcoholic". He is initially surprised at KG's utterance and then recounts it later to a friend as a slightly depreciatory "joke" on him by the patient. He noted he is "very pleased" with her progress on the intra-nasal insulin treatment. In one sense, then, the patient is now creating new words with new meanings [48] a treatment-mediated illocutionary achievement in its own right.

The patient's exact illocutionary intent in this instance does raise the question of whether it is just a metathesis or also a witty play on words. Tirumalesh (1991) notes, the orientation of "re" words in pragmatic terms eludes exact formalization [48]. Either way, however, the utterance had a positive perlocutionary effect as the listener interpreted it as an utterance said with biting wit (a joke). INI has been shown to reach the neural basis of humor processing which engages a core network of cortical and subcortical structures, including temporo-occipito-parietal areas involved in detecting and resolving incongruity [50,4].

Section IV

Empathy & Self-Awareness

The emergence of perlocutionary effects also relates to illocutionary capacity in the domains of empathy and self-awareness. Expressing empathy for the other person and validating and agreeing with the other's persons feelings are all effects that a person might want to achieve through a specific communication interaction.

The following vignettes at two months of treatment¹¹ illustrate KG's growing capacity to use words appropriate for the circumstances and to express empathy. For example, while watching a Hallmark movie ("When Comes the Heart") where a person dies, KG spontaneously stated: "They love each other. That is really sad," "He is sad, his

wife is dying" and asked: "Is he dying too"? At another instance during the same movie, KG even used figurative language (an idiom). She stated to her sister-in-law who was also watching the movie, with regard to a male character who was behaving inappropriately toward a woman, "He is giving her a real line". After an emotional scene in the tele series "Anee with an E", KG said appropriately: "Very touching".

Perlocutionary effects also express sincerity (intention) or the conditions necessary for the utterance to have the intended effect. One morning during the shower ritual when her sister-in-law was rinsing her off, KG spontaneously produced an utterance with the intended perlocutionary effect of thanking her, stating: "You work hard". Other expressions of empathy at two months include when the patient after her brother fed her, was cleaning up and passed by KG on the couch, she said to him very clearly: "I love you."

At eight weeks of treatment, self-awareness and pragmatic capacities also improved from baseline. KG was able to accurately recite the Lord's prayer word by word with her brother in their nightly bedside routine. Conversely, during her first month of treatment, she was only able to mouth the words. On another occasion when her brother was administering the INI treatment to her, she sought to be helpful and assist, asking him: "Want me to get closer to you"? On another occasion, KG expressed self-awareness of her own visual condition and a heightened desire to participate socially. When her caregiver ironically commented, "I'm having a bad hair day", KG immediately stated: "Well you can fix mine too".

This growing self-awareness also manifested in increasing sophisticated conversational "give and take". This particular pragmatic response was initially noted [3] when a patient's wife described how her husband responded to INI in the first months. She noted: "The differences [with treatment] were subtle but they were cumulative. They are undeniable...I am with my husband again. Whereas before it was...um... (head gesture) ...I don't want to say somebody who needed to be taken care of but (pause)...there wasn't any give and take as far as conversation was concerned. It changed our whole outlook".

Similarly, KG's sister-in-law noted that KG was talking more and that many of her comments were appropriate to the situation. Indeed, at two months of treatment, KG's sister-in-law even communicated to KG a concern about her own pregnant daughter and received an empathic reply. She relayed: "I told KG we were concerned about Kelly's high blood pressure which might make her have the baby early. KG immediately replied, 'I'll pray for her.' Here KG is able to successfully produce an utterance in the present with the

¹⁰Metathesis is the transposition of syllables or sounds in a word or of words in a sentence. Most commonly, it refers to the interchange of two or more contiguous sounds in a word, known as adjacent metathesis [49]. Examples include: foliage > **foilage, cavalry > **calvary. KG's metathesis was uttered at 4 ½ weeks after INI treatment began.

¹¹The patient's daily dosage was increased to .40ml twice daily at 7 weeks.

intended perlocutionary effect of trying to reduce to suffering of the another (by praying).¹²

This latter pragmatic communication exchange shows intention (sincerity), empathy and an immediate appropriate verbal response ("I'll pray for her"). At two months of treatment, it demonstrates how KG is now immediately able to grasp and respond appropriately terms to the distress in her sister-in-law's discourse.

Section V

Pragmatic Competence under Treatment

Our case study shows the rapid improvement of pragmatic competence in a patient in several areas even after 12 weeks of treatment. It strongly suggests INI treatment could be an independent target for therapeutic improvement in its own right even in moderate to late-stage AD.

Specifically, several aspects of the recovery of pragmatic (illocutionary/perlocutionary) functions targeted for therapeutic improvement in moderately severe AD are illustrated. For example, the immediate return of illocutionary effect and ability to express sincerity ("I like this, Can I help you?") and bodily needs ("I am cold, I have poops, I do not want to get out of bed") occurred within the first days and weeks of treatment. Such treatment-mediated enhanced pragmatic capacities provided multiple opportunities for meaningful communication with the patient. Next, KG's visually-based episodic memory retrieval led her to spontaneously declare ("That's my brother' friend!" and "I remember that!"). Her newfound ability to respond to cued speech by family members ("I" ... "Love" ... (pause) Patient: "Lucy". "Who is your favorite movie star"? Patient: "Elizabeth Taylor"), in turn caused the very positive perlocutionary effects on her sister-in-law who responded with laughter, pleasure ("That's right!" "Yes", very pleased, smiling). These pleasurable conversational exchanges further reduce social withdrawal common to AD. Improved communication thereby reduces the social isolation of the patient and improves the likelihood of successful care at home.

¹²Similarly, AR, at year 4 of extended INI treatment (although he never recovered short-term memory recall which was zero at baseline) [4], was still able on multiple occasions to grasp the emotional complexity of a situation and to respond deeply by verbal empathy. When his daughter recounted to him that her husband had committed suicide that year, AR said: "That is awful. Why did he do that? That is so terrible", "That must be so hard", "I am sorry you are now a widow". Then AR would be unable to recall his son-in-law's death within 20-30 minutes of the communication exchange although he had attended his son-in-law's funeral that earlier year. This occurred each of the three times his daughter leaned on him for emotional support around the death and he listened and responded empathically and appropriately to his daughter's suffering. Each time, however, she had to recall to him that the event had happened and its details [29].

After two months of treatment, the patient became increasing able to express higher-level social emotions. In terms of pragmatic competence, this was evident in her ability to "give and take" in conversational exchanges which showed intention (sincerity), gratitude ("I love you") and an immediate appropriate verbal response in response to another's emotional distress ("I'll pray for her"). These represent speech acts whose illocutionary force includes the display of empathy and further encourages bonding. KG's capacity to use words appropriate for the circumstances also revealed treatment-mediated enhanced pragmatic competence with respect to executive-functioning (paying attention). For example, her comments to sad parts of a TV series ("They love each other, that is really sad," "He is sad, his wife is dying") and her relevant questions ("Is he dying too?") were emotionally on-track according to her sister-in-law. In contrast, Hsieh et al (2013) argues that in AD, the ability to perceive another person's emotional state, to respond emotionally and to take the perspective of others has been found to decline with progress of the disease [51].

Typically, clinical descriptions of moderate to late AD speech describe them as "verbose and circuitous, yet empty and lacking meaningful content" [52]. KG's treatment-mediated illocutionary ability to verbalize self-deprecatory humor in response to song lyrics illustrates meaningful, focused self-awareness of her own limitations--"That (falling in love) is not going to happen", "I am not having fun". These illocutionary achievements are consistent with increased activity in the rAI and its association with music to heighten emotionally laden moments [36]. Self-deprecatory humor is also a self-oriented pragmatic response. It can have the perlocutionary effects of, variably, achieving appreciation, sympathy and even love, enabling a person to grapple actively with the fear his/her weakness arouses in him/her. It can even function in a defensive way, to protect a person from negative experiences (loss of love) [53]. In this instance, it resulted in KG's sister-in-law finding these comments "interesting".

Schatz & Rivera (2016) argue that INI treatment-mediated improvements in pragmatic competence in MCI and early to moderate AD suggest that cognitive impairment should not just be understood as processes and domains related mostly to memory (short/long term recall) [8]. They should also be understood to include improvements in perception, language, self-awareness and awareness of others. This is illustrated in one extended INI patient with moderate AD and zero recall at baseline whose pragmatic competence, executive functioning, and visuo-spatial tests improved significantly. Yet he also displayed very uneven memory even after several years of INI treatment [5]. For example, this patient remembered that he had quit smoking when he was 30 years old but did not remember he had a daughter who lived out of state. In this article, KG, with her moderately severe AD diagnosis at baseline, was able to recognize her mother in an old home video. Yet, she would

also state: “I don’t have any children” (she has 2 sons who rarely visit her) (treatment week #6).

Improved illocutionary force and perlocutionary effects in these domains reflect rising communicative sophistication with caregivers even in latter disease stages. KG began pre-treatment with monosyllabic, often incorrect responses with little or no motivation to do anything other than lie in bed. She then progressed to more actively watching movies and being able to verbalize emotional feelings that characterize human sentience (love, empathy, concern, thanks, humor) during the first three months of INI treatment. The patient even gained the illocutionary ability to verbalize a metathesis in conversational exchange with the visiting handyman--“Are you tired or re-tired?” This, in turn, had the perlocutionary effect on the listener of teasing wit (a joke). Similarly, in the social realm, her spontaneous desire to participate interactively occurred when her caregiver said, “I’m having a bad hair day”, KG stated: “Well you can fix mine too”. Her increasing ability to accurately comment on other’s emotion during movies watched with caregivers also foster positive interactions that support pragmatic competence. KG’s increasing ability to listen and respond verbally and empathically to caregivers (“I’ll pray for her”, “Thank you for what you are doing”) also reflect mutually satisfying higher levels of real communication for caregivers with the patient as a person with an identity (albeit an amnesiac one).

With respect to executive functioning, this article finds again the description (either by patients or their family member and caregivers) of “coming out of a fog” just after the patient’s initial INI treatments. This metaphor suggests complex post-treatment changes, along with give and take in conversation, signs of a reversal of apathy associated with lvPPA, and a newfound attentional focus on TV or movie watching. Also evident was an increase in social participation, improved mood and less irritability [3,8].

Thus, INI appears able to engender a conjunction of changes: pragmatic (rising illocutionary/perlocutionary capacity), emotional (empathy, bodily/self-awareness), cognitive (paying attention), social (reengagement) even in the later stages of AD. KG’s revitalization, from nearly total linguistic, emotional, attentional and even gustatory apathy is succinctly summed up in a conversational vignette. It was the first time that her brother had heard her communicate in three full, consecutive sentences rather than just in single words (“You sure are eating a lot. I want to eat a lot like you too? Where can I get some food?”). He noted that “before (INI) treatment, it was a losing battle, all downhill...She often refused to eat, and, was dying and trying to starve herself to death. Now (at 1 month of treatment), she eats, eats, eats like a horse”.

The neuroanatomical implications of the improvement of pragmatic competence point toward INI’s immediate effects on the insular cortex, thalamus and areas of the brain related

to executive functioning. The insular cortex contains the primary gustatory, visceral cortex and, in humans, a unique thalamo-cortical extension into the right anterior insula (rAI) cortex¹³. This extension engenders distinct bodily feelings of pain, temperature, visceral sensations, hunger, thirst, state and sensual touch [36]. Activation of homeostatic afferent activity in the rAI also results in higher level social emotions such as empathy, empathic pain (which are directly related to subjective interoceptive awareness), and, by extension, emotional depth and complexity [36]. Executive function is, by definition, inextricably associated with the various cognitive, linguistic and sensorimotor elements in the intrapersonal domain over which it exercises control [7]. Executive functions and inference require simultaneous attention and the ability to process multiple sources of information in parallel. Future research is necessary to pinpoint the exact neuroanatomical correlates of nose-to-brain pathways of intra-nasal insulin and its functional impacts on improved pragmatic competence in advanced AD¹⁴.

Increased pragmatic capabilities within a context of continued significant cognitive limitations do alter the more typical power relationships of discourse contexts of AD patients with their caregivers [22]. For example, KG’s heightened self-awareness caused a shift in night care as she began to vocalize complaints about being woken up to be taken to the bathroom. KG began to complain to her brother: “What are you doing”? “You can’t get me up”, “I don’t want to get out of bed”. Before treatment, she would just get up. Nevertheless, because her short-term memory is so

¹³The thalamus is a central mechanism in understanding and formulating language and is also relevant to “cognition” through the “specific alerting response” (SAR) [54, 55, 4] Pragmatics, in particular, relies on both left and right hemispheres and the thalamus mediates from the superior temporal cortex and posterior parietal cortex, or the “language eloquent cortex in humans [56, 57]. The thalamus, in its capacity as a relay mechanism, is a region of the brain where the administration of INI significantly increased perfusion by 6.5% ($p=0.003$) when compared to placebo [39]. An analysis of extended INI patient “AR’s” CT scans over five and a half years of treatment showed that areas of the brain associated with pragmatic competence, e.g., slower atrophy rates in occipital and thalamic structures as compared with the structural imaging of patients with disease progression from MCI to AD not receiving intranasal insulin therapy [4]. Both the activity and physical size of the rAI affect individual subjective awareness and the thalamus relays afferent activity from its source in the nucleus of the solitary tract (NTS) [36]. Increased cerebral blood flow to the insular cortex and putamen due to INI (Schilling et al, 2014) augments neuronal signaling due to increased energy demand of active neurons which in turn leads to vasodilatation around the active area [58].

¹⁴In terms of the effect of INI on improving executive functioning receptors in Phelan-McDermid Syndrome, it is hypothesized that its mechanism is enhancing neuronal function by increasing CNS glucose uptake and synaptic plasticity [44, 45]. Glucose is the primary source of energy for brain cells, and the brain cells of AD patients are starved for energy [29]. PET scans showed glucose uptake and utilization is dramatically decreased in patients with AD [59]. Intranasal insulin also increases brain cell energy (ATP & Phosphocreatine) in humans as demonstrated with 31-P-MRI. Alzheimer’s disease has been shown to involve an insulin and IGF-I signaling deficiency in the brain [60].

compromised, her brother is able to coax her now, saying to her: “We will stay a few more moments” and then she complies¹⁵. At the same time, the easing of caregiver burden in the area of incontinence is also part of KG’s positive treatment-mediated changes. At 13 weeks, KG’s incontinence improved markedly for the first time, with the patient being dry for two nights (at intervals of 5 h). The patient also began to verbalize the accurate need to use the restroom; another indication of rising bodily self-awareness. Her enhanced attentiveness to the TV, focus on eating, and self-awareness of her own limitations also indicate improvements in executive functioning skills and visuo-spatial functioning related to INI treatment [5].

CONCLUSION

KG’s results are the first systematic examination of INI on pragmatic competence in later AD stages. The capacity of a moderately severe AD to shift from near total aphasia (pre-treatment) to immediate (post-treatment) verbal responsiveness and then rising illocutionary is an important discovery in the effects of INI on pragmatic competence. Our model examined pragmatic units as both utterance elements and as units incorporating cognitive and socio-interactive dimensions, which are essential in the determination of the success of the perlocutionary and illocutionary functions associated with speech acts. The focus on pragmatic competence, even in moderate to late-stage AD, finds that intra-nasal insulin can affect a conjunction of changes: linguistic (self-deprecatory humor, sarcasm), emotional (empathy, bodily/self-awareness), cognitive (paying attention) and social reengagement. This model of pragmatic competence under targeted treatment supports the hypothesis of enhanced neuronal activity in relevant brain areas associated with subjective interoceptive awareness (bodily and emotional depth and complexity). It strongly suggests that INI treatment could be an independent target for therapeutic improvement in its own right especially in reducing AD-related aphasia and apathy. Increasing the pragmatic capacities of the patient significantly improves communication exchanges with caregivers, thereby reducing their endemic stress even in later disease stages.

ADDITIONAL INFORMATION

KG is one patient from an open-label study of a series of 150 MCI and AD patients from which qualitative findings on the

compassionate use of intranasal insulin have been reported. Before ViaNase delivered treatment, these patients displayed significant symptoms of social and linguistic withdrawal, flattening of affect, and irritability. Family reported caregiver stress was moderate to high. KG began her twice daily dosage at .20IU of insulin for 7 weeks in late March 2020, then increased to 40IU twice daily.

Several previous quantitative studies exist on 153 MCI and AD patients involved in the short-(4 months) and medium-term (12 months) administration of intranasal insulin using the ViaNase device to deliver the drug exist. They jointly confirm the findings of the preservation of caregiver-rated functional ability in MCI and AD patients. The first randomized, placebo-controlled pilot study of ViaNase delivered intranasal insulin consisted of 104 adults with amnesic mild cognitive impairment (n = 64) or mild to moderate AD (n = 40), all of whom were treated with 20 and 40 IU daily dosages of intranasal insulin for 4 months.¹⁶ The mean patient age was 71 years old, and the mean MSE score was 83.7–84.3 [20 IU/40 IU]. 50–57% were positive for the high-risk apolipoprotein E epsilon-4 allele. The results show that treatment with 20 IU of insulin improved delayed memory (P <.05), and both doses of insulin (20 and 40 IU) preserved caregiver-rated functional ability (P <.01). Both insulin doses also preserved general cognition as assessed by the ADAS-cog score for younger participants and functional abilities as assessed by the ADCS-ADL scale for adults with AD (P <.05). “Placebo-assigned participants showed decreased flude oxyglucose F 18 uptake in the parietotemporal, frontal, precuneus, and cuneus regions and insulin-minimized progression [2].

The second placebo-controlled study of ViaNase delivered intranasal insulin administration consisted of 49 of 289 patients with mild cognitive impairment (MCI) or mild Alzheimer’s disease (AD) who were randomized to receive either insulin or placebo daily for 12 months [61]. This was a phase 2/3 trial at 26 US sites and a change in cognitive function from baseline to 12 months served as the primary endpoint, with the primary outcome using the Alzheimer’s Disease Assessment Scale-Cognition measure (ADAS-Cog 12). The ViaNase delivered intranasal insulin slowed the annual progress of cognitive decline by 50%—or only a 2.5-

¹⁵Limited recall also continues to foster unclear and/or poor judgement. For example, AR with a moderate AD diagnosis at baseline was able to engage in verbal play, teasing, metaphors and self-deprecatory humor until his death. Yet, he was unable to understand or to use judgement (a cognitive deficit) as why he had to wear his sleep apnea mask and let caregivers put it back on repeatedly in the middle of the night. This was something he never used to forget or not attend to before his AD diagnosis [8]. Fortunately for KG, her brother viewed his sister’s increased pragmatic capacity to vocalize her demands for autonomy within a context of gratitude as “good”, and so much better than the previous “fog” she was in pre-treatment.

¹⁶Assessments were made at baseline and at 3-month intervals until the end of the study, when participants were offered open-label insulin treatment for another 6 months. The other 240 patients used a different device (Precisions Olfactory Delivery [POD]) which failed to produce any difference in outcome on the ADAS-Cog 12 measure at 12 months with the placebo group. Both POD and placebo groups increased by about 4 points on the ADAS-Cog 12 measure, indicating worsening. Nor were there any changes in any other Alzheimer-related biomarkers like amyloid-beta 40 and 42, total tau, or phosphorylated tau (Clinical Neurology News 12/4/18:2). The model is controlled for age, sex, genetic risk status, and investigation site. Patients were a mean of 71 years old, with a mean Mini Mental State Exam score of 25. Around 42% were positive for the high-risk apolipoprotein E epsilon-4 allele.

point decline per patient on the ADAS-Cog12 versus the 5-point decline per patient of the placebo group. This significant “separation was evident at 3 months and continued to widen over the course of the [12 month] study [61]”.

As long-term efficacy is always a concern in insulin treatment, the only published CT scan of a patient on long term INT is included with this additional material section. This patient “AR” received extended INI for 5 ½ years [4] **Figure 1a** is AR’s CT scan at 5 years INI therapy (5 ½ years after AD diagnosis, 4/18). **Figure 2a and b** show subcortical segmentation of MRI scans, after boundary correction, of a

subject classified as MCI (2a) and of a subject diagnosed with probable Alzheimer’s disease (2b) [62]. AR’s CT scans demonstrate that his occipital lobe does not show a significant shrinkage of grey volume (indicated by black arrow, **Figure 1a**). Similarly, AR’s thalamus, indicated by yellow arrow (**Figure 1a**) is “also not as atrophied in terms of volume loss as the AD patient (**Figure 2b**) despite AR’s frontal volume loss and lateral ventricle enlargement consistent with late stage AD. [63,4].” [AR’s earlier CT scans (at MCI diagnosis and at 3 ½ years after treatment began) can be viewed in detail at [4].

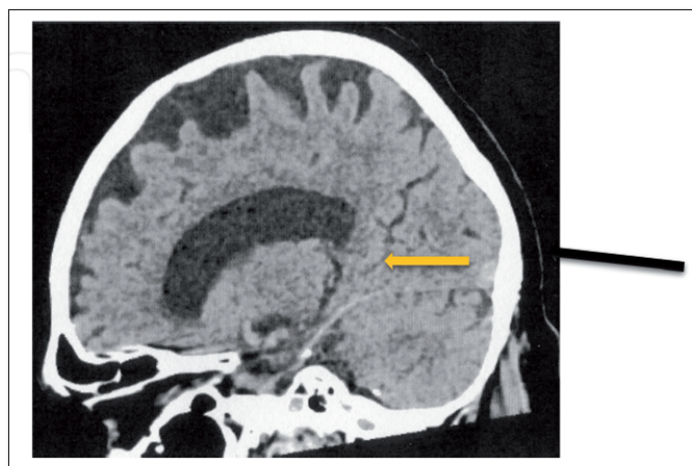


Figure 1a. CT scan of extended INI patient at 5 years of treatment.

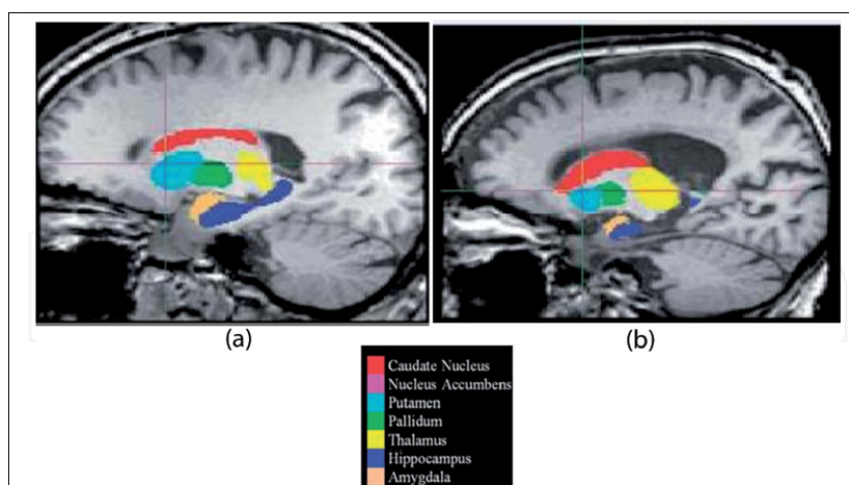


Figure 2. Sub cortical segmentation of MRI scans, after boundary correction, of (a) a subject classified as MCI, (b) and of a subject diagnosed with probable Alzheimer’s disease [62].

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