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Intranasal Insulin as Promising Therapy for Preserving Pragmatic Competence in MCI and AD

Sara Schatz

Abstract

Our chapter contends that extended intranasal insulin administration can preserve pragmatic functioning even when there are temporal lobe and frontal lobe brain volume losses consistent with AD disease progression. CT scans of a patient receiving extended intranasal insulin 6 years after AD diagnosis are compared with his CT scans at the original MCI diagnosis. The results demonstrate that areas of the brain associated with pragmatic functioning were not as affected as expected in late-stage AD patients. This, along with linguistic evidence of preserved pragmatic competence, indicates the likely effectiveness of intranasal insulin treatment in enhancing neuronal activity in certain areas of the brain associated with pragmatic competence.

Keywords: MCI, intranasal insulin, brain atrophy, pragmatics

1. Introduction

This chapter explores, on a brain circuitry level, why patients receiving extended intranasal insulin therapy continue to be able to ambulate independently, pay attention, speak, and participate in jokes even throughout late-stage AD [1–3]. We find that extended intranasal insulin administration can preserve pragmatic functioning even when there are temporal lobe and frontal lobe volume losses consistent with Alzheimer's brain (AD) volume loss. A series of CT scans of a patient receiving extended intranasal insulin from mild cognitive impairment (MCI) diagnosis and those from the same patient 5.5 years after AD diagnoses are examined. At baseline, this patient's original MCI CT scans indicated no significant intracranial pathology and normal aging brain morphology. Over time, we show how this patient demonstrates 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. Enhancing neuronal activity in the areas of the brain associated with pragmatic competence reduces the likelihood of anomia typical of late-stage AD.

This chapter is structured as follows: Section 1 examines studies of the perfusion of intranasal insulin in older adults concerning neuropsychiatric tests of cognitive decline in MCI and AD. Section 2 discusses CT scans and the medical and social history of the patient case study used in this chapter. Section 3 examines CT scans at three distinctive points in the patient's MCI to AD progression (at MCI diagnosis and 3.5 and 5.5 years receiving intranasal insulin therapy). Section 4 suggests that results demonstrating extended intranasal insulin treatment may slow disease progression

by reducing some areas of neuronal atrophy in the (thalamus) cortico-pulvinar projection system associated with the anomia typical of late-stage AD.

2. The perfusion of intranasal insulin in context

In MCI and AD, the intranasal delivery of insulin has been found to enhance brain insulin activity either through improved glucose metabolism or reducing hypothalamic inflammation [4]. The route of intranasal insulin to the central nervous system (CNS) is via the olfactory and trigeminal neural pathways which innervate the nasal cavity and provide a direct connection to the CNS [5]. Given the short time frame (15–30 minutes) by which intranasal insulin reaches the brain, it is assumed that extracellular delivery from the nasal mucosa, instead of axonal transport, is the main transport mechanism. Glucose metabolism abnormality is thought to play a critical role in pathophysiological alterations by inducing multiple pathogenic factors such as oxidative stress, mitochondrial dysfunction, glycolysis, and Krebs citric acid cycle [6]. By pharmacologically restoring disrupted brain insulin signaling that ensues from glucose insufficiency [7], intranasal insulin is thought to promote neuron survival.¹

Recent studies of the perfusion of intranasal insulin into the regional areas of the brain cortex demonstrate two main regional cortical areas of penetration. Akintola et al. [10] found that, in older adults, intranasal administration of insulin significantly increased perfusion through the occipital gray matter by 6.5% ($P = 0.001$) when compared to the administration of placebo as well as perfusion into the thalamus ($P = 0.003$). Perfusion through the parietal gray matter was also increased by 4.3% after administration ($P = 0.034$) in older adults.

According to the authors, increased perfusion strongly suggests that intranasal insulin therapy might restore energy demand and neuronal activity in these regions. They note:

We observed that intranasal insulin application increased perfusion of the thalamus. The thalamus receives information from almost all sensory systems and relays the information to associated cortical areas. From literature, increased cerebral blood flow has been linked to vasodilatation around the active area due to increased energy demand [11]. Also, insulin has been shown to be a vasoactive modulator that regulates peripheral and cerebral blood flow possibly via a direct vasodilatory effect [12]. Taken together, our finding of increased perfusion in some brain areas would support the hypothesis that intranasal insulin application might restore energy demand and neuronal activity in these regions [4, 10].

2.1 The thalamus and occipital structures in language, attention, and visuospatial tasks in Alzheimer's disease

The thalamus is a central mechanism in understanding and formulating language [13]. It passes information from one cortical area involved in language generation to another, including semantic feature binding and the generation of

¹ Delivery of IGF-I to the CNS is thought to be beneficial in the treatment of Alzheimer's disease or stroke because of IGF-I's ability to potentially promote neuronal survival [8]. In adult rat CNS, regions of the circumventricular organs (choroid plexus and median eminence), olfactory system (olfactory bulb, anterior olfactory nucleus, and primary olfactory cortex), frontal cortex, hippocampus, amygdala, cerebellum, and spinal gray matter exhibit the highest concentration of IGF-I binding sites [9]. In a recent study, Sami et al. show that intranasal insulin treatment moderately increases glucose uptake in the WT mouse hippocampus via activating the Akt2 signaling pathway.

lexical items [14]. Pragmatics, in particular, relies on both the left and the right hemispheres, and the thalamus mediates from the superior temporal cortex and posterior parietal cortex, or the “language eloquent cortex” in humans [15, 16].

The thalamus is also relevant to “cognition,” which includes the capacity to pay attention and to process multiple channels of information at once, i.e., to engage in “intentionally guided attention” or “engagement in action” [17]. An explicit mechanistic model has even been developed for thalamic stimulation effects on language and cognition that incorporate modern activation and connectivity data called the “specific alerting response” (SAR). The SAR effect involves secondary switching in the striatum caused by the activation of thalamostriatal projections, whereas the “anomia effect” implicates the disruption of the cortical synchronization action of the pulvinar via the cortico-pulvinar-cortical projection system [18].² In this SAR model, the retained ability to speak (an “anti-anomic” effect) depends upon the preservation of nuclei within the thalamus to regulate the transmission of information to the cortex and between cortical areas [21]. As such, the thalamus acts as a “selective engagement mechanism” which suppresses right frontal cortical activity, preventing it from interfering with language [17]. As Crosson [22] notes:

“in other words, once an intention to act is formed, the frontal lobes engage the cortical nets relevant to the intended activity. For example, if one intends to engage in a conversation, frontal cortex associated with language, via the nucleus reticularis and the pulvinar, engages cortices related to understanding and formulating language. At the same time, areas not involved in the intended activity would be held in a state of relative disengagement so as to minimize attention to stimuli irrelevant to the intended task.”

In Alzheimer’s disease, it is well recognized that the thalamus is essential for generating attention [23], and its anterior and medial nuclei are involved in declarative memory functioning [24]. Anatomic evidence from AD patients shows that thalamic volume reduction in Alzheimer’s disease has been related not only to anomia but also to global cognitive decline in all of these areas: motor behavior, emotional, motivational, associative, and cognitive abilities [25]. Nevertheless, until de Jong et al. [26], the direct correlation between measurements of decreasing thalamic volume and cognitive functioning in Alzheimer’s disease had never been reported in the literature.

Intranasal administration of insulin also significantly increased perfusion through the occipital and parietal gray matter in older adults [10]. The occipital lobe is the visual processing center of the mammalian brain containing most of the anatomical region of the primary visual cortex. It also contains the ventral stream of vision that enables ability to focus on motor actions in response to outside stimuli. The parietal lobe is a source of speech and reading. Next to the occipital lobe, the parietal lobe integrates sensory information among various modalities, including proprioception, mechanoreception, and visuospatial processing. The posterior parietal cortex, also referred to as the dorsal stream of vision, receives somatosensory and/or visual input that can be transmitted to motor signals [27].

In MCI and AD, impairments in the dorsal stream of visual perception and processing have been found to be a predictor of AD [28]. Increasing impairment in visuospatial skills, visual object processing, and visual recognition of human

² The functional and anatomic evidence supports the assertion that the connectivity of the pulvinar is the likely nucleus to mediate communication of information [18]. The pulvinar is heavily connected to the cortex and forms cortico-thalamo-cortical pathways. As a general principle, directly connected cortical areas will be indirectly connected via the pulvinar [19, 20].

emotion processing are common on test scores of AD patients as part of annual cognitive deterioration [29–31]. Previous studies of MCI and AD patients receiving extended intranasal insulin have demonstrated unusual patterns of relatively limited annual cognitive declines as measured by several years of neuropsychiatric batteries. This was the case in tests covering visuospatial skills and executive function and inference tests which required simultaneous attention and the processing of multiple sources of information in parallel such as the VOSP Number Location, Pentagons, Modified Rey, CATS-Fact, and Affect Matching tests [2]. Furthermore, the short-term administration of intranasal insulin (21 days) has been found to significantly improve response inhibition on discordant items of an executive function-attention test (the Stroop test) [32, 33]. In addition, visuospatial function was significantly improved in performance on the Benton Visual Retention Test (BVRT) after 40 IU of insulin detemir, regardless of apoe4 status [32, 34].

Observational data on one patient receiving extended intranasal insulin therapy showed that even 5.5 years after AD diagnosis, he was still able to walk independently, pay attention to his physical surroundings, process visual information, and make verbal inferences [2]. Another patient who began intranasal insulin at MCI/mild dementia diagnosis after having lost the ability to manage his finances, shop, or independently go to doctor's visits returned to being able to do all of these tasks and even to going skiing after 3 years on treatment.

3. CT scans and progression from MCI to AD

Computed tomography (CT) is a structural medical imaging method that employs computer-based tomographic reconstruction to delineate bodily structures based on their ability to block X-ray beams. CT images are used to identify structural abnormalities, such as space-occupying lesions or intracranial neoplasms, although CT images are less fine in detail than newer structural imaging technologies [35].

The key CT structural markers of disease development in the progression from MCI to AD include atrophy rate measurements in the hippocampus and medial temporal lobe (the inner part of the temporal lobe, near the divide between the left and right hemispheres) [36]. In addition, ventricular enlargement of portions of the lateral ventricles adjacent to the medial temporal lobe (MTL) is also a sensitive marker of the transition from MCI to AD [37–39]. Thus, in the disease progression from MCI to AD, hypometabolism in glucose uptake leads to increased atrophy rates of lateral ventricles adjacent to the MTL and to a reduction of hippocampal volume and then to the temporal neocortex. Finally, the disease progresses into adjoining association and primary sensory areas [40, 41].

The medial temporal lobe in particular is thought to be involved in declarative and episodic memory. Deep inside the medial temporal lobe is the region of the brain which includes the hippocampus, the amygdala, the cingulate gyrus, the thalamus, the hypothalamus, the epithalamus, the mammillary body, and other organs, many of which are of particular relevance to the processing of memory. Studies of single-dose intranasal insulin demonstrate that intranasal does reach the hypothalamus but these results did not reach statistically significant levels ([10]:793). Other single-dose studies of intranasal insulin to diabetics showed acutely increased resting-state functional connectivity between the hippocampal regions and multiple regions within the DMN, i.e., the medial frontal cortex; the medial, lateral, and inferior parietal cortex (IPC); and anterior (ACC) and posterior cingulate cortex (PCC). These are brain regions directly linked to interactive higher

cognitive functions [42]³ including language. The uncus,⁴ an anterior extremity of the parahippocampal gyrus, a deep structure within the limbic system of the MTL, is of central importance in protecting/rescuing hippocampal neurons from amyloid-induced neurotoxicity [43, 45, 46].

Conversely, patients on extended intranasal insulin should demonstrate slower rates of atrophy as the insulin restores energy demand and neuronal activity in occipital and parietal gray matter regions and the thalamus [10]. CT scans over the AD disease course of a patient receiving extended intranasal insulin can be hypothesized to illustrate patterns closer to “normal aging” of MCI even 5–6 years after AD diagnosis (see also Additional materials). Thus, it can be hypothesized that AD patients receiving extended intranasal insulin therapy may demonstrate slower atrophy rates in occipital and thalamic structures than MCI to AD patients not receiving this therapy.

3.1 Case study: social and medical history

A series of three CT scans were conducted on patient “AR” between May 2012 and April 2018. AR was between the ages of 82 and 88 during this time and was 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. The patient was moved out of state in September 2017 when his 82-year-old girlfriend developed Parkinson’s disease. He subsequently lived near his daughter in an Alzheimer facility and was seen by a qualified university neurologist until his death in December 2018.

The patient initially became involved in the compassionate use of twice-daily intranasal insulin for the purposes of reducing cognitive decline in June 2013. 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 or with minor assistance throughout the course until the final months of his life when he needed assistance with cutting up his food (8/18–12/18). During the years of 2012–2017, AR was still able to live in his home with his 80-year-old girlfriend who cooked, shopped, and drove him to their social activities, and his financial and medical management was done

³ Zhang et al. [42] found that intranasal insulin-treated diabetic subjects performed better on the visuospatial memory task (BVM-T-R) and on verbal fluency naming tasks. The former tended to correlate with stronger connectivity between the left hippocampal region and PCC. Better performance on the verbal fluency naming task was associated with stronger coefficient of connectivity between the right hippocampal region and ACC and lesser connectivity between the left hippocampal regions and the MFC for a more difficult category switching task. As Zhang et al. [42] summarize: “Differences in relationships between cognition and connectivity between the right and left hippocampal regions were found which reflect a complexity of the large-scale verbal fluency network that comprises of verbal fluency and orthographic discrimination subnetworks...Set switching is a complex operation involving a number of different brain structures that usually include various parts of the dorsolateral and dorsomedial prefrontal cortex, as well as temporal regions where hippocampus is located.”

⁴ The uncus is a rudimentary, small area where the frontal lobe meets the temporal lobe and the area of cortex on the uncus of the parahippocampal gyrus (both belonging to the olfactory cortex). It is phylogenetically older (the so-called paleocortex) and is part of the limbic system. The uncus is connected to the olfactory tract through nerve fibers which bend abruptly toward it and is separated from the apex of the temporal lobe by a slight fissure called the incisura temporalis. Given its centrality in early MCI [43], it is necessary to ascertain potential structural and/or diffusional and cellular barriers to intranasal insulin penetration into the surrounding CNS tissue and significant clearance of CSF into the venous and lymphatic circulation [44].

by his daughter [2]. While residing in his Alzheimer residence facility (11/17–12/18), AR was still ambulatory, fed himself, ate with the early AD patients at the dining room, and was highly conversational even at this stage of disease progression [3].

AR's medical history at MCI diagnosis was (5/12) OSA, diverticulosis, tinnitus, lumbar stenosis, and BPH. His medications were memantine, donepezil, tamsulosin, multivitamin, and intranasal insulin (at 6/13). At 10/16, the same medications, all blood work normal.⁵ At 4/18, the same medications, all blood work normal. At 4/18, 5.5 years after his original AD diagnosis and at age 88, his doctor stated to AR's daughter that the patient was still "very functional with good language skills" and, to the doctor's surprise, still possessed "the body of a 70-year-old" [3].

4. Results

4.1 At MCI diagnosis: before beginning intranasal insulin therapy

AR was diagnosed with MCI in May 2012 based on a Slums test score (24/30) and a mild cognitive impairment AD8 score = 0/8. His neurologists stated: "The patient came in because he had begun to not remember essential tasks, lost his keys and had begun to become disoriented at times. For example, he could not remember the proper freeway exit for the airport or where he was on the freeway despite having driven to that airport on that same route for over 40 years. Patient himself feels memory not so good. He was also beginning to forget the names of plants at the botanical gardens which he once knew he could. His girlfriend thinks his memory issue may be out of the ordinary in forgetting day to day conversations [47]."

CT scans were ordered due to this "altered level of consciousness." The initial CT findings of AR's neurologist at this time stated there was "no significant intracranial pathology" with "normal aging brain morphology." All other CT findings were also "normal," i.e., "intact (calvarium, central skull base, temporal mastoids: adequate; cellular, non-sclerotic, paranasal sinuses: well aerated; brain showed no acute intracranial bleed, large vessel territory infarct, or mass effect) (CT Results 5/12)."⁶ B-12 and TSH levels were also in normal limits (5/12). Indeed, the overall assessment of AR's 5/12 CT scan was summarized succinctly as "changes of aging brain."

In terms of his memory loss, however, the neurologist's findings were more uncertain. He noted: "Robust looking man. Gait brisk, very cordial and engaging and gives detailed history but when asked his profession, he seemed to have to think awhile before he recalled he was a science teacher." Clearly AR's neurologist detected something was amiss when he stated: "While patient score is in the mild cognitive impairment range, and while he is very intellectually active: plays bridge, studies German, goes folk dancing still I think he should be scoring higher than he does. While I cannot make a diagnosis of Alzheimer's now, I think we need to follow up in 6 months and see how it goes [47]."

Nevertheless, CT at 5/12 *did* show markers of disease progression toward AD. AR's CT scan includes the following analysis: "Ventricles are 'prominent' as there are subarachnoid spaces within cerebrospinal fluid." Ventricular enlargement represents a feasible short-term marker of disease progression in subjects with MCI

⁵ Full blood work results available upon request. (10/16): BP 121/58 mmHg | Pulse 84 | Temp(Src) 98.7°F (37.1°C) | Resp 18 | Wt 189 lb. 6 oz. (85.9 kg) | SpO2 98%. Ext: WWP; no leg swelling/asymmetry/edema; 2+ bilateral symmetric radial pulses; no calf swelling/TTP/cord [47].

⁶ CT HEAD. Technique: Contiguous noncontrast transaxial images from the vertex to the skull base were obtained. Estimated phantom dose: CTDIvol (mGy): 29 DLP (mGy-cm): 501. Consider follow-up limited brain FDG-PET evaluation (PET scan) to work up dementia, if clinically indicated.

and subjects with AD because portions of the lateral ventricles are adjacent to the medial temporal lobe (MTL), structures that atrophy notably in the preclinical stages of dementia [38, 48]. Nestor et al. [49] even hypothesize that ventricular dilatation after 6 months would differentiate normal aging, MCI, and MCI to AD progressors and be a more sensitive measure of disease progression than cognitive scores. For example, they found subjects with AD had a 60% greater ventricular enlargement than subjects with MCI and a fourfold enlargement compared with normal aging as measured over a 6-month interval. Jack et al. [50] argue that hemispheric atrophy rates, measured by ventricular enlargement, correlate more strongly with changes on cognitive tests than medial temporal lobe (MTL) atrophy rates and capture significant variation between subjects with MCI and AD [37, 39]. The rate of ventricular volume change is also highly correlated with an increase in senile plaques and neurofibrillary tangles [51].

In AR's case such ventricle enlargement was, in fact, a sensitive measure of disease progression. Six months later in his follow-up visit (12/18), AR's Slums score had dropped by 4 points to 20/30, and his AD8 score increased by 1 point to 1/8. Even more disease progression was evident in cognitive measures of his short-term memory: AR scored 4/8 in story recall and had a 0/5 recall of objects 5 minutes later [47]. At this point in time, December 2012, AR's neurologist diagnosed him with early AD. He noted: "Impression and plan: It is now clear that this is early Alzheimer's. Will begin Aricept. Gave information on Alzheimer's disease and referral number of our incredibly skilled and compassionate memory clinical social worker. Follow up on 3–4 months [47]."

4.2 3 1/2 years after diagnosis: 3 years on intranasal insulin: still looks more like MCI

AR, in conjunction with his family, made the decision to begin intranasal insulin therapy in June 2013, 6 months after his 12/12 AD diagnosis. At this point, his MMSE score was 24 (3/13), and his word recall after 10 minutes was 0/9 (3/13) [2]. The patient's functional abilities had also markedly deteriorated from a year previous at his 5/12 MCI diagnosis. AR could no longer manage his finances or his medical treatments and could no longer drive. His family also noticed the development of significant social and linguistic withdrawal, irritability, and flattened affect ([1]:331–333). For example, AR expressed very little positive emotion upon seeing his daughter and granddaughter at the airport after a 6-month separation. Furthermore, he was unable to participate in conversations or even access anything about himself such as how he was feeling, often remaining silent for extended periods of time, and withdrawing from social engagement ([1]:331–333).

The patient's family began compassionate use of intranasal therapy (6/13) at twice daily for AR (20 IU per dose). Over the subsequent 6–8 months of treatment, they noticed a marked return of pragmatic functioning, an increase in social and linguistic participation (even returning to telling and understanding jokes), self-awareness, and decreased irritability ([1]:333–35). AR himself reported just 2 days after beginning therapy that his head hurt less, spontaneously holding his head with his hand and stating to his daughter: "Oh, it is like I have had a terrible headache for a long time."

A return of meaningful linguistic interaction after intranasal insulin therapy and a stabilization of the further deterioration were also noted by other patient's family members after several months. This stabilization was reflected in his 2014 and 2015 neuropsychological battery of tests. These cognitive tests revealed a marked slowing of annual percent decline in executive function and visuospatial scores compared with average annual declines [2, 31]. AR also was able to use and respond affectively to humor in conversations, related areas of the brain typically associated with significant deterioration in AD progression [52].

A CT scan was taken on AR in October 2016, just over 3 years after the patient began receiving intranasal therapy (**Figure 1a** and **b**). Again, the overall neurologist's impression was "age-related volume loss." The record reads:

Comparison: "Comparison is made with 05/17/2012. There is no evidence of intracranial hemorrhage, mass, mass effect, large infarct or midline shift. Prominence of the ventricles and sulci are noted, likely age-related volume loss. Scattered periventricular white matter hypodensities are noted, most commonly seen with small vessel ischemic changes. Vascular calcifications are noted. Partial opacification of the ethmoid and sphenoid sinuses noted. Bones are unremarkable. Impression: No evidence of acute intracranial process. *Age-related volume loss*. Likely small vessel ischemic changes [47]."

This diagnosis of "age-related volume loss" after 3 years receiving intranasal insulin suggests some positive effects of extended therapy. AR's neurologist noted in his 10/16 comments that the patient was: "alert and oriented" with "5/5 strength in all 4 extensions with full distal sensation; no saddle anesthesia; 2+ symmetric reflexes throughout and ambulates without difficulty [47]."

Figure 1a and **b** shows evidence of AD disease stage progress. For example, in his 10/16 notes, AR's neurologist comments on the "prominence of the ventricles and sulci" which are more enlarged (the ventricles) and deeper (the sulci in the frontal lobe) (**Figure 1a**) than AR's 5/12 MCI diagnosis CT scan (**Figure 2**). Furthermore, AR's memory was very uneven; he stated that he quit smoking when he was 30 years old but did not remember his daughter who lived out of state.

Further clarification of the positive effects of intranasal insulin therapy at 3 ½ years after his AD diagnosis can be observed comparatively. **Figure 3** shows a structural MRI of the typical progressive atrophy (of medial temporal lobes and hippocampus) in an older cognitively normal (CN) subject, an amnesic mild cognitive impairment (aMCI) subject, and an Alzheimer's disease (AD) subject. In this disease progression from MCI to mild AD, the hippocampus of the subject in **Figure 3** shows marked atrophy as indicated by the white arrows. Hippocampal atrophy, especially left volumes, and its contribution to memory decline in the process of Alzheimer's disease have been often described and are widely accepted [53, 54].

In contrast, AR's CT scan (**Figure 1a**) shows a hippocampus size that is still relatively robust. As indicated by the white arrow in **Figure 1a**, AR's left hippocampus is similar to that of the patient in **Figure 3** at MCI disease stage. **Figure 1a** and **b** also shows significantly less overall frontal cortex atrophy, medial temporal lobe atrophy, and occipital lobe atrophy as compared with disease progression of the MCI to

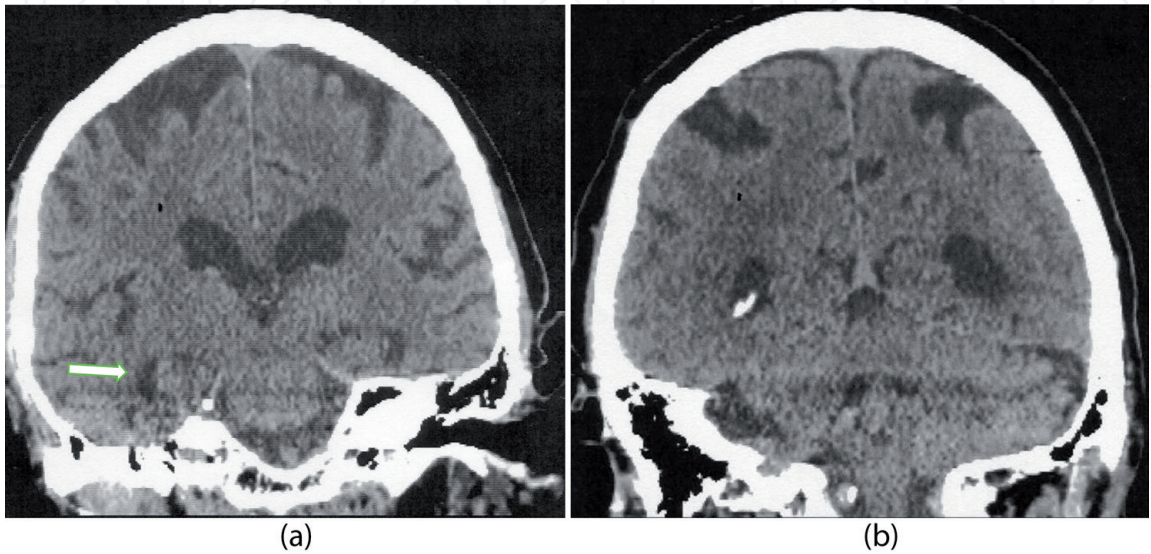


Figure 1.
(a) and (b): CT scans of patient AR, 10/16.



Figure 2.
CT scan of patient AR, 5/12.

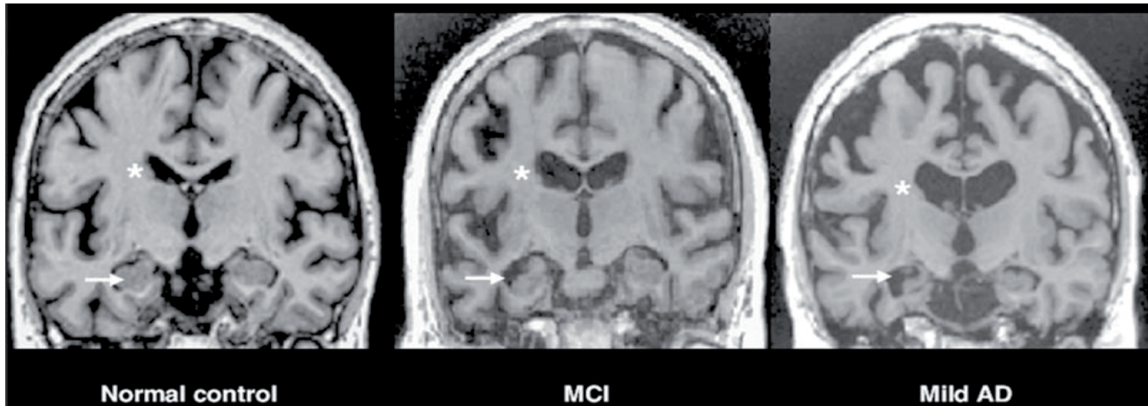


Figure 3.
Structural MRI of the typical progressive atrophy (of medial temporal lobes and hippocampus) in an older cognitively normal (CN) subject, an amnesic mild cognitive impairment (aMCI) subject, and an Alzheimer’s disease (AD) subject.

AD patient (**Figure 3**). These are significant positive effects of extended intranasal insulin as illustrated in AR’s 10/16 CT scan.

A return of meaningful linguistic interaction after intranasal insulin therapy and a stabilization of AR’s executive functioning test scores also reflect his neurologist’s overall interpretation of “age-related” (vs AD disease progression related) volume loss in his 10/16 CT scan. AR’s executive functioning capacities at year 4 after AD diagnosis include still being able to actively watch a TV series in several 45-minute episodes. In addition, on one occasion, when a scratched DVD disk caused the episode to pause, AR was able to immediately alert his daughter of the need to fix the problem. This demonstrates that AR was actively paying attention [2]. Prolonged attention span was found across patients with Phelan-McDermid syndrome after 1 year receiving intranasal insulin [55].

Another patient diagnosed with mild AD improved his executive functioning area scores (immediate recall, delayed free recall, and animal recall scores) after 8 months receiving intranasal insulin [2]. As Sperling et al. [56] note, AD causes considerable damage to the neurobiological substrate of episodic memory, the hippocampal-entorhinal complex (located in the medial temporal lobes) early in the course of the disease. After several years receiving intranasal insulin therapy, the patient continued

to demonstrate capabilities in visual processing skills (occipital and parietal lobe functioning) as well as improvements in executive functioning under targeted therapy. At 3 years, he had returned to being able to ski (2019) after having lost the ability to manage his finances, shop, or independently go to doctor’s visits [2].

4.3 5 ½ years after AD diagnosis and 5 years on insulin therapy: less atrophy of occipital and thalamic structures

At year 5 ½ after AD diagnosis and at 5 years receiving intranasal insulin therapy (12/17–12/18), AR was still able to inferentially reason. He was also fully ambulatory, eating with the mild AD patients at his nursing home, and looked at books and TV while paying attention to both. His visual skills were also still intact. For example, one day AR was walking independently back to his room with his daughter and headed toward a large automatic opening and closing door to the Alzheimer wing which was being held open by a staff member. AR immediately turned to his daughter and asked: “Can we go through?” His daughter responded: “Yes.” Then AR was able to remember, proceeded to analyze contextual information and to simultaneously warn her of possible impending danger, telling her: “Hurry up. It closes fast” [3].

Figure 4 is AR’s CT scan at 5 years receiving intranasal insulin therapy (5 ½ years after AD diagnosis) (4/18). **Figure 5a** and **b** presents subcortical segmentation of MRI scans after boundary correction of a subject classified as MCI (4a) and of a subject diagnosed with probable Alzheimer’s disease (4b) [26].

Consistent with our hypothesis that extended therapeutic usage should slow AD disease progression, AR’s 4/18 CT scans demonstrate that his occipital lobe does not show a significant shrinkage of gray matter volume (indicated by black arrow, **Figure 4**). Similarly, AR’s thalamus, indicated by the yellow arrow (**Figure 4**), is also not as atrophied in terms of volume loss as the AD patient (**Figure 5b**) despite his significant frontal volume loss and lateral ventricle enlargement consistent with late-stage AD [50].

AR’s retained volume in the occipital and thalamic subcortical structures supports previous findings that intranasal insulin directly reaches the occipital cortical brain regions and the thalamus in older adults [10]. These results suggest such enhanced insulin action in these brain areas can, in fact, slow AD disease progression.

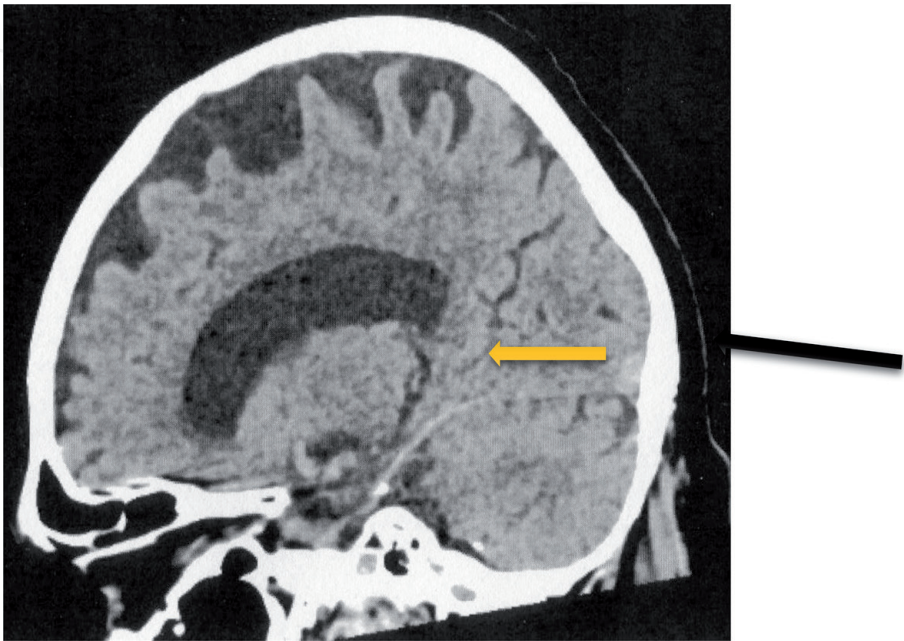


Figure 4.
CT scan of patient AR, 4/18.

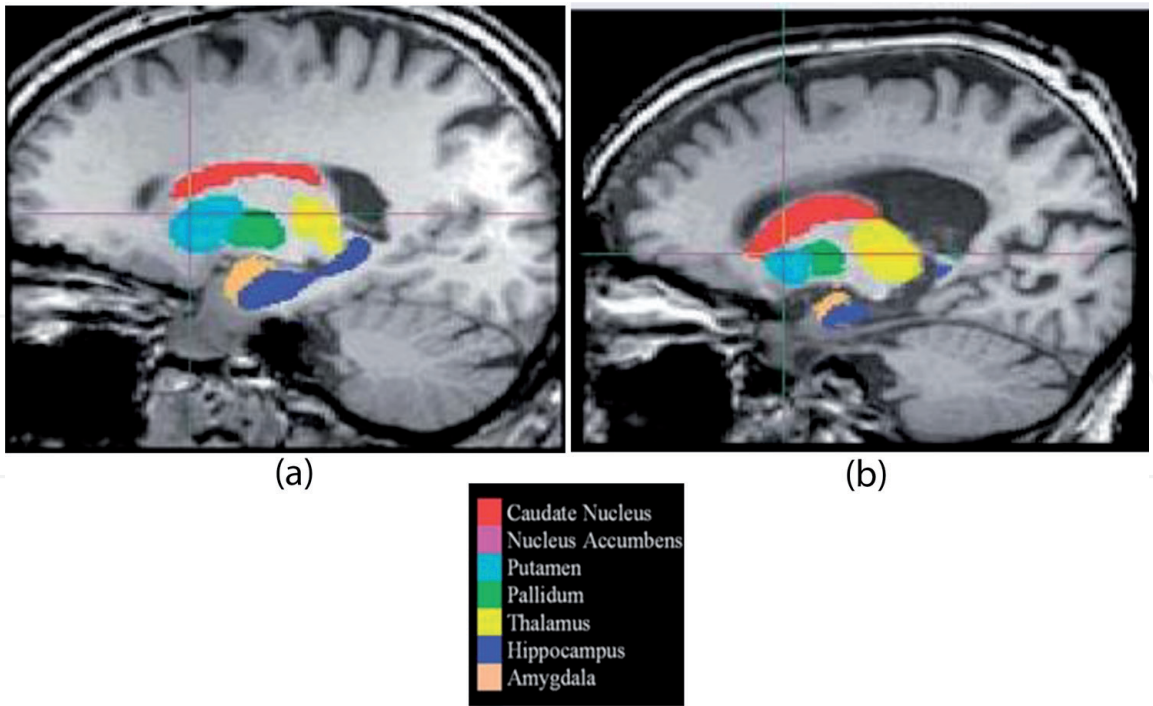


Figure 5.
(a) and (b): subcortical segmentation of MRI scans, after boundary correction, of a subject classified as MCI (a) and of a subject diagnosed with probable Alzheimer's disease (b) (sagittal view) [26].

Figure 6a and b demonstrates how AR clearly shows signs of advanced AD by 4/18. AR's neurologist noted of his 4/18 CT scan:

“Lateral ventricles are 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 disproportionate frontal and temporal lobe volume loss. This includes medial temporal lobe volume loss with likely considerable hippocampal volume loss especially on the right. Sulci are not symmetrical on both sides [47].”

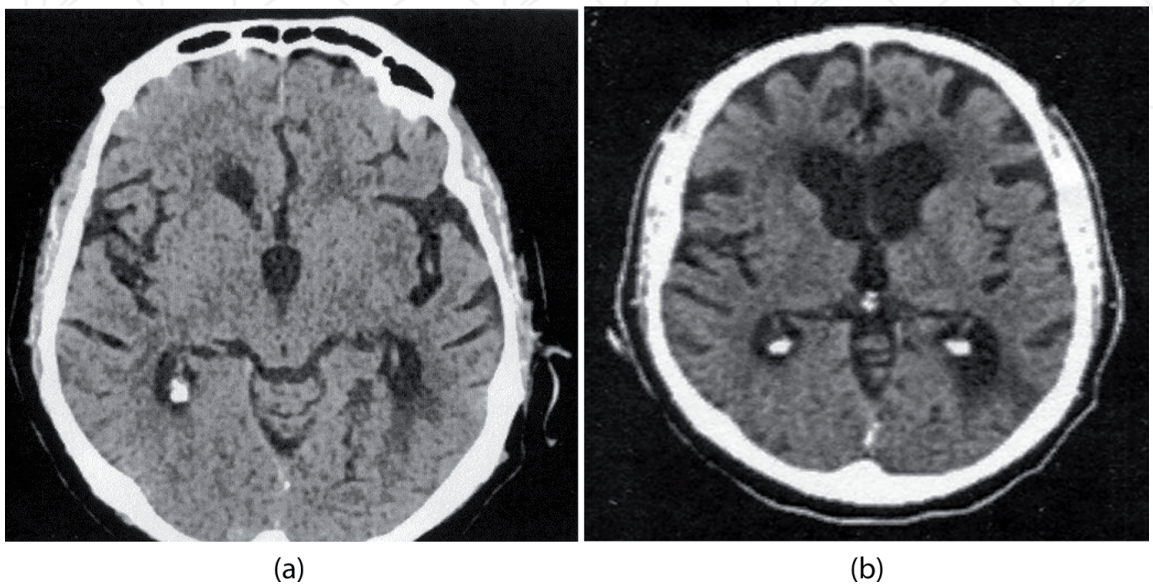


Figure 6.
(a) and (b): CT scans of patient AR, 4/18.

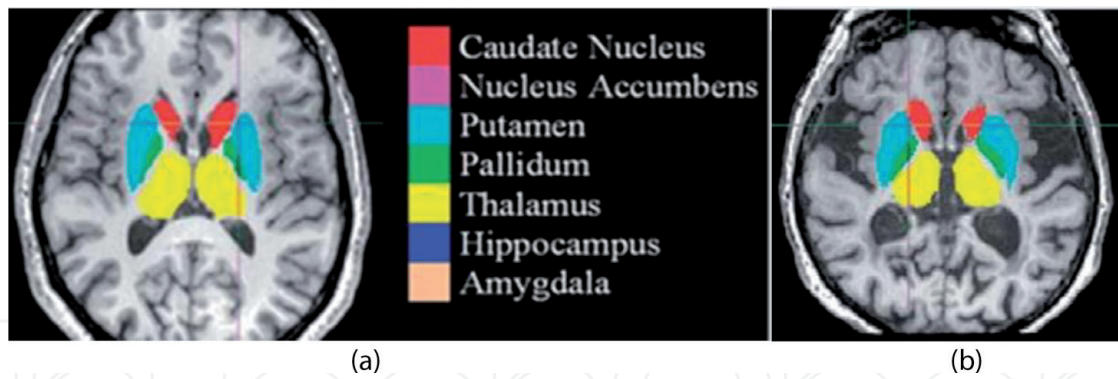


Figure 7. (a) and (b): subcortical segmentation of MRI scans, after boundary correction, of a subject classified as MCI (a) and of a subject diagnosed with probable Alzheimer's disease (b) (axial view) [26].

Yet, as (again) compared with probable AD (**Figure 7b**), AR demonstrates less overall volume loss even with respect to the medial temporal lobe. Furthermore, in AR's case, left hippocampus atrophy is less pronounced than right (**Figure 6a** and **b**). This is also a significant finding because, as de Jong et al. [26] found in their Alzheimer's disease group, volume reduction of the *left* hippocampus, putamen, and thalamus formed the strongest predictors for declining cognitive performance in Alzheimer's disease progression.

5. Discussion

The potential of intranasal insulin to curb the development and progression of AD [57] is by avoiding decreases in cerebral glucose metabolic rate within a complex neuronal network which comprises the hypothalamus, hippocampus, thalamus, and cortical brain structures. A series of CT scan results of a patient receiving extended administered intranasal insulin usage shows delayed atrophy of key areas of the brain associated with cognitive, visual, executive, and pragmatic functioning as compared to disease progression in MCI to AD patients not receiving therapy. These findings, particularly those that demonstrate slowed atrophy of the thalamus and occipital lobe, strongly suggest that extended intranasal insulin treatment might slow disease progression by reducing some areas of neuronal atrophy in the (thalamus) cortico-pulvinar projection system [18] associated with the anomia typical of late-stage AD [58, 59]. They also highlight the importance of thalamic stimulation on language and cognition and the ability of the preservation of nuclei within the thalamus to regulate the transmission of information to the cortex and between cortical areas [21]. The reduced atrophy of the occipital lobes in this patient on extended intranasal insulin therapy is also significant because lesion studies have shown that the pulvinar is critically involved in visual perception, attention, and visually guided behavior [21], which can include directing visual attention to a cued location.

The slowing of atrophy of the thalamus is also consistent with the hypothesized medial pathway of insulin [2, 3, 60] in which the thalamus is reached via the olfactory tubercle. Future research is required to refine precisely how intranasal insulin promotes glucose utilization in these neuronal networks, i.e., through changes in hippocampal synaptic plasticity and/or by increasing synapse density and dendritic plasticity in structures that process visual input ([61]:216).

Future follow-up studies are needed to explore how intranasal insulin's potential effectivity for reducing transition rates from amnesic MCI to AD is related to preserving those neurological structures associated with pragmatic tasking.

Specifically, additional studies are required consisting of mapping out the bulk flow of intranasal insulin along the olfactory and trigeminal pathways between the nasal passages and the CNS into deeper structures within the medial temporal lobe (MTL) ([45, 62]:491). The region of the MTL showing the greatest atrophy in mild cognitive impairment is the entorhinal cortex, which is precisely part of the parahippocampal gyrus and is the same region that has been postulated by Braak and Braak [40] to be the site where AD pathology is first expressed.

Additional practical studies are necessary to understand the relationship between the olfactory system and the delivery route of intranasal insulin on such hippocampal structures within the MTL to further elucidate the potential of intranasal insulin therapy. AR's continuing pragmatic abilities including sarcastic utterances, utilizing empathic tone and pragmatic discourse markers [3] 6 years after AD diagnosis and 5 ½ years on intranasal insulin, point toward the partial effect of intranasal insulin on deeper hippocampal brain structures. The right parahippocampal gyrus, for example, has functions beyond the contextualizing of visual background stimuli and identifying social context such as the inclusion of paralinguistic elements of verbal communication resulting in the ability to employ sarcasm [63]. As Smith [43] notes:

Many years (up to 50) before the symptoms (of AD) occur, neurofibrillary tangles start to form in neurons in the parahippocampal gyrus. At some stage, this process is exacerbated, and many projection neurons in the MTL then start to die, leading to atrophy of the lobe and to early signs of memory deficits. Once denuded of their input from the MTL, neurons in the target areas of neocortex show reduced activity, leading to slower metabolism and a fall in local blood flow. They will no longer function properly in the neural networks underlying higher cognition [64].

The findings in this chapter also illustrate, on a brain circuitry level, AR's other continued pragmatic capacities even with late-stage AD [2, 3]. Several weeks before his death from a post-hip surgery-related heart attack, AR was still able to employ a bodily related metaphor: "I am tired. It seems like that is all I say. What a pain in the ass that is." This statement involves the capacity to abstract and inhibit literal interpretation, both of which are associated with executive functioning tasks. Other linguistic evidence of AR's preserved pragmatic competence even 5.5 years after his AD diagnosis include telling jokes and using humor to assert autonomy [1–3]. The capacity to detect, understand, and respond to humor deteriorates significantly in the progression of AD [65]. Scholarship on the neural basis of humor processing precisely suggests that humor engages a core network of cortical and subcortical structures, including temporo-occipito-parietal areas involved in detecting and resolving incongruity [66]. The temporo-parietal junction incorporates information from the thalamus, among other systems.

Treatment-induced improvements in neuronal activity in the thalamus and occipital and parietal lobes can bring moderate to significant improvements in communication exchanges with caregivers, thereby reducing the AD patient's social and communicative isolation, lessen caregiver stress, and improve executive functioning. Furthermore, AR's annual, standard blood tests did not reveal abnormalities or indicators of chronic intranasal insulin therapy leading to (further) desensitization of his brain insulin signaling [67] a concern expressed in the literature [57].⁷

The results contained in this paper are the first published CT scans of a patient receiving extended intranasal insulin use. Begun at early MCI diagnosis, the extended use of intranasal insulin could substantially impact sites along the

⁷ Future studies can measure this potential through recent exosome biomarker tests derived from blood, plasma, and serum for the detection of brain insulin signaling resistance [68, 69].

olfactory pathway (hypothesized to be affected early on in AD).⁸ This could potentially arrest the further spread of the disease process in the involvement of the hippocampus, areas of the neocortex in the parietotemporal and frontal lobes, as well as hypothalamic inflammation linked to age and disease-related declines in insulin sensitivity [4, 46]. One patient after 8 months of intranasal insulin was administered a series of pre- and post-therapy neuropsychological tests, including visuospatial skills, visual spatial ability, visual working memory, and executive functioning after beginning intranasal insulin [2]. Eight months later, his neurologist concluded that: “There was about a two-year reversal of cognitive impairment while receiving intranasal insulin, going from mild dementia to mild cognitive impairment [3].” A return to MCI from early AD is a significant therapeutic achievement that deserves further application and investigation.

Additional materials

Several previous studies 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 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 (9). The mean patient age was 71 years old, and the mean 3MSE score was 83.7–84.3 [20 IU/40 IU]. 50–57% were positive for the high-risk apolipoprotein E epsilon-4 allele. The following results were reported: “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 ($P < .05$). Cerebrospinal fluid biomarkers did not change for insulin-treated participants as a group, but, in exploratory analyses, changes in memory and function were associated with changes in the A β 42 level and in the tau protein-to-A β 42 ratio in cerebrospinal fluid. Placebo-assigned participants showed decreased fludeoxyglucose F 18 uptake in the parietotemporal, frontal, precuneus, and cuneus regions and insulin-minimized progression.” 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 [70].⁹ 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 measuring the Alzheimer’s

⁸ In the olfactory system, the sites that are affected include the anterior olfactory nucleus, the uncus, and the medial group of amygdaloid nuclei—all receives fibers directly from the olfactory bulb ([69]:4534).

⁹ Assessments 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.

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-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” [71].

The finding in this chapter of the reduction of caregiver stress after the longer-term administration (3 plus years) of intranasal insulin is also evident from qualitative findings from an open-label study of 22 MCI and AD patients on the compassionate use of intranasal insulin.¹⁰ These patients displayed, before ViaNase delivered treatment, significant symptoms of social and linguistic withdrawal, flattening of affect, and irritability, as well as moderate to high levels of family-reported caregiver stress [1–3, 60]. Several publications also extensively document treatment-mediated improvements in language, visuospatial, and, in particular, executive functioning test scores of patients at moderate AD and an early MCI patient (5) and a return of pragmatic competence in the areas of jokes, self-expression, and empathy in early and moderate AD and MCI patients [1, 60]. Over 90% of caregivers of the 22 compassionate use patients also reported moderate to very strong reductions in caregiver stress after 1 year of intranasal insulin administration to their family members [1, 60, 73, 74].

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¹⁰ These MCI and AD patients live in naturalistic settings (2011–present) and provide linguistic evidence on phenomena as they naturally occur, i.e., they provide conversational data for the case study methodology as used by sociologists for the purpose of theory development and building. Hamilton [72] found that it is only in such conversations that it is possible to describe the full range of communicative competence of a person with AD.

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