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Review

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Neurobiological Differences Between Aggression and Agitation in Persons with Dementia

Ladislav Volicer[1,*]

[1]School of Aging Studies, University of South Florida, Tampa FL, USA

Abstract

Background

Controversy exists about definition of agitation and especially about inclusion of aggression as a part of agitation in people with dementia.

Methods: Papers describing neurobiological indices related to behavioral symptoms of dementia were reviewed. Papers comparing indices in persons exhibiting aggression and persons exhibiting agitation were selected for this review.

Results

The survey found seven papers which compared neuroanatomical indices and three papers which compared neurochemical indices. The neuroanatomical indices differentiating agitation and aggression included changes in brain perfusion, sizes of brain areas, distribution of neurofibrillary tangles, and white matter changes. The neurochemical indices differentiating agitation and aggression included relationships with neurotransmitter variables and the cell count in the locus coeruleus.

Conclusion

Despite the small number of papers and some methodological problems, the presented information clearly indicates that aggression and agitation are two distinct unrelated syndromes in persons with dementia.

Corresponding author: Ladislav Volicer, School of Aging Studies, University of South Florida, Tampa FL, USA 2337 Dekan Lane Land O'Lakes, FL 34639, Telephone: 813-909-0539, Email: lvolicer@usf.edu

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Introduction

Behavioral and psychiatric symptoms of dementia are very common and are often more distressing than consequences of cognitive impairment. These symptoms are associated with increased healthcare use, earlier institutionalization [1]. excess morbidity and mortality, greater caregiver distress and depression [2]. While the psychiatric symptoms are well defined and use uniform terminology, there is a confusion about terminology of behavioral symptoms. While the group of experts, convened by the International Psychogeriatric Association (IPA) defined agitation as a behavior "manifesting excessive motor activity, verbal aggression, or physical aggression" [3], other authors separate agitation and aggression and consider them as two separate syndromes, which may coexist in one individual but not at the same time [4,5].

Separation is of aggression and agitation is based on different circumstances present when these syndromes occur and several rating scales, including MDS 3.0 make this distinction [6,7]. Aggression is overt behavior of animals or humans involving intent to harm another organism or inanimate object.[8] while agitation may be defined as "Motor restlessness, heightened responsivity to stimuli,irritability, inappropriate and/or purposeless verbal or motor activity, decreased sleep, and fluctuation of symptoms over time." [9] that may occur when the person with dementia is solitary and does not interact with others. Although majority of IPA experts decided that aggression is a part of agitation, they did not have any scientific basis for this conclusion. The aim of this paper is to provide information indicating that separation of aggression and agitation is supported by differences in neuroanatomical and neurochemical changes occurring in these two syndromes.

Methods

Medline was searched using "dementia AND behavior AND brain changes AND people". The search identified 811 publications. By reviewing abstracts of these publications, [17] were selected for detailed review of the methods used in the study. In 10 papers, methods used by the investigators clearly differentiated between aggression and agitation and were included in this study. Several scales were used by investigators and Table 1 lists items of these scales which were used to indicate aggression or agitation. It is important to recognize that the names of domains in some scales are confusing. That is especially true for the Neuropsychiatric Inventory (NPI), where item Agitation/ Aggression measures resistiveness to care which may escalate to combative behavior and reactive aggression. That item Agitation/Aggression is measuring resistiveness to care is especially clear from description of this item in NPI-NH version (Table 1) and in NPI-Q version where the only question is "Is the patient resistive to help from others at times, or hard to handle?" [10,11].

Results

There were several differences in neurobiological substrates found in persons who exhibited agitation and in persons who exhibited aggression. These differences were detected in both clinical and post-mortem studies (Table 2, Table 3)

Clinical Studies

Differences between aggression and agitation included changes in brain perfusion, differences in brain atrophy, and white matter changes. Hirono et al [12] compared the pattern of regional cerebral perfusion determined by single photon emission computed tomography in 20 patients with dementia with behavioral symptoms measured by the NPI. Of the 10 aggressive patients with dementia 8 were diagnosed as having Alzheimer's disease (AD), and 2 were diagnosed as having vascular dementia. Of the 10 nonaggressive patients with dementia 8 were diagnosed as having AD, 1 was diagnosed as having dementia with Lewy bodies, and 1 was diagnosed as having normal pressure hydrocephalus. Patients with aggression had significant hypoperfusion in the left anterior temporal cortex, bilateral dorsofrontal and right parietal cortex while there was no correlation between perfusion and agitation.

Burns et al [13] measured several areas of the brain by computed tomography in 178 patients with Alzheimer's disease. In these subjects, 29% exhibited aggression and 18% agitation. They found that aggression was significantly related to temporal lobe atrophy while wandering was related to increased size of the Sylvian fissure.

Rosen et al [14] investigated relationship between sizes of selected brain areas and behavioral symptoms of dementia in 148 patients with dementia

Table 1. Definitions of aggression and agitation by the scales used in this review

Scale	Aggression	Agitation
Cohen-Mansfield Agitation Inventory (CMAI) [24]	Physical /Aggressive Hitting (including self) Kicking. Grabbing onto people. Pushing. Throwing things. Biting. Scratching. Spitting. Hurting self or others. Tearing things or destroying property. Making physical sexual advances Verbal /Aggressive Screaming. Making verbal sexual advances. Cursing or verbal aggression	Physical /Non-Aggressive Pace, aimless wandering. Inappropriate dress or disrobing. Trying to get to a different place. Intentional falling. Eating / drinking inappropriate substance. Handling things inappropriately. Hiding things. Hoarding things. Performing repetitive mannerisms. General restlessness Verbal/Non-aggressive Repetitive sentences or questions. Strange noises (weird laughter or crying). Complaining. Negativism. Constant unwarranted request for attention or help
Neuropsychiatric Inventory (NPI) [25]	C. AGITATION/AGGRESSION Upset with caregiver; resists ADL's Stubbornness Uncooperative; resists help Hard to handle Cursing or shouting angrily Slams doors; kicks, throws things Hits, harms others [36]	J. ABERRANT MOTOR BEHAVIOR Paces without purpose Opens or unpacks closets or drawers Repeatedly dresses and undresses Repetitive activities or "habits" Handling, picking, wrapping behavior Excessively fidgety
Present Behavioral Evaluation (PBE) [37]	2. Aggressive behaviour Aggressive resistance - resisting attempts to help or being uncooperative, usually in the context of intimate care Physical aggression - eg hitting, kicking, scratching, pushing or spitting in an aggressive manner Verbal aggression and hostility -speaking in an aggressive or cross tone or voice raised in anger	1. Overactivity Walking more - walking distinctly more than is normal Aimless walking - walking aimlessly without an obvious reason Trailing and checking - needing frequent reassurance of presence of carer either by following or frequently checking location of carer
Stockton Geriatric Rating Scale (SGRS) [38]	Behaviour resulting in or liable to result in actual physical harm to another person	Walking more, aimless walking, and trailing and checking

Table 2. Neurobiological indices related to aggression and agitation

Clinical studies		Scale used	Reference
Aggression	Agitation		
Hypoperfusion in the left anterior temporal, bilateral dorsofrontal and right parietal. cortices	No correlation with perfusion	NPI *	12
Termporal lobe atrophy	Widening of Silvian fissure	SGRS**	13
Not related to any tissue loss	Tissue loss in the right dorsal anterior cingulate cortex and left premotor cortex	NPI	14
No relationship with size of amygdala	Amygdala atrophy	NPI	15
No correlation	Correlated with white matter hyperintensi-ties	NPI	16
Post-mortem studies			
Increased NFTs in hippocampus	No correlation with hippocampal morphology	PBE***	17
Increased NFTs in the left orbitofron-tal cortex in left anterior cingulate	Increased NFTs in the left orbitofrontal cortex only	NPI	18
Decreased acetylcholine and choline acetyltransferase in frontal and temporal cortices	Decreased serotonin levels in frontal cortex	PBE	19
No correlation	Correlations with neurotransmitter variables in hippocampus and cerebellum	CMAI****	21
Low cell count of the locus coeruleus	No correlation with cell count	PBE	22

* Neuropsychiatric Inventory [25]

** Stockton Geriatric Rating Scale (SGRS) [38]

*** Present Behavioral Examination (PBE) [37]

**** Cohen-Mansfield Agitation Inventory (CMAI) [24]

Table 3. Types of scales measuring behavioral and psychiatric symptoms in dementia

Domain	Method for data collection	
	Proxy report	Observation
Single behavioral syndrome	Ryden Aggression Scale [39]	Scale for Observation of Agitation in Persons with DAT [dementia of the Alzheimer type] (SOAPD) [40]
	Caretaker obstreperous-behavior rating assessment (COBRA) scale [41]	Resistiveness to Care – Dementia of the Alzheimer Type (RTC-DAT) scale [42]
All behaviors	Cohen-Mansfield Agitation Inventory (CMAI) [24]	
	Present Behavioral Examination (PBE) [37]	
Comprehensive assessment	NPI [25], NPI-NH [36], NPI-C [29], NPI-Q [11]	Minimum Data Set 3.0, E0300 Overall Presence of Behavioral Symptoms, E0800 Rejection of Care [7]

using voxel-based morphometry. Dementia diagnoses included frontotemporal dementia (FTD) (n = 39), semantic dementia (n = 23), progressive non-fluent aphasia (n = 13), corticobasal degeneration (n = 12), progressive supranuclear palsy (n = 9) and Alzheimer's disease (n = 52). Of these subjects, 44% exhibited agitation/aggression, and 40% aberrant motor behavior. Aberrant Motor Behavior was related to tissue loss in the right dorsal anterior cingulate cortex and left premotor cortex while Agitation/Aggression was not related to tissue loss in any area.

Similarly, Poulin et al [15] who used magnetic resonance imaging (MRI) in 264 subjects with very mild and mild Alzheimer's disease and 180 controls, found that greater amygdala atrophy was associated with more prominent aberrant motor behavior, but not with scores on other NPI items (delusions, hallucinations, euphoria/ elation, disinhibition, sleep and appetite).

Aggression and agitation were also separated in a white matter study. Hirono et al. [16] studied 76 AD patients who had white matter hyperintensities (WMHs) but no obvious cerebrovascular diseases. They quantified the volume of WMHs by using fast-fluid–attenuated inversion recovery images. They found that WMHs were related to Aberrant Motor Behavior and Disinhibition, while Agitation/Aggression item was not related.

Post-Mortem Studies

Two studies reported increased load of neurofibrillary tangles (NFTs) in aggressive subjects with dementia. Lai et al [17] examined hippocampi of 27 subjects who had premortal evaluation of their behaviors by the Present Beavioral Evaluation (PBE). Of the 27 patients, 21 were neuropathologically confirmed to have Alzheimer's disease whereas three patients were determined to have vascular dementia. One patient had mixed vascular dementia and Alzheimer's disease, another had an unusual tauopathy, and one had nigral cell loss and evidence of ischaemic hippocampal damage. Using factor analyses of the point of entry interview data, three component behaviours have been identified for aggression (physical aggression, verbal aggression, aggressive resistance to intimate care) and overactivity (walking more, aimless walking, trailing and checking) syndromes. The investigators found that neurofibrillary tangles were significantly elevated in subjects with history of aggressive behavior while there was no difference in neurofibrillary tangle density in subject with and without chronic overactivity.

Tekin et al [18] examined postmortem brain of 31 subjects with diagnosis of AD, who had NPI evaluation before death. They found that Agitation/ Aggression item was related to NFT burden in the left orbitofrontal cortex and left anterior cingulate, while Aberrant Motor Behaviors showed a significant relationship with NFT density only in the left orbitofrontal cortex.

There are several neurotransmitters that are affected differently by aggression and agitation. Garcia-Alloza et al [19] examined post- mortem brains of 22 patients with clinical diagnosis of dementia and 20 elderly normal controls matched for age, gender, post-mortem delay and brain pH, who were evaluated by the PBE before death. Their results showed that aggressive behavior scores were the best predictors of lowered choline acetyltransferase (ChAT) and acetylcholine esterase (AChE) levels in both frontal and temporal cortices, while overactivity factor was the best predictor of serotonin (5-HT) reductions in the frontal cortex.

Vermeiren et al [20] did an extensive study measuring concentrations of dopamine, 5- HT, norepinephrine, and respective metabolites using reversed-phase high performance liquid chromatography in brains of 40 neuropathologically confirmed AD patients. They found several correlations between neurochemical parameters and non-aggressive behaviors; in the hippocampus with 5-hydroxyindoleacetic acid (5-HIAA) levels, homovanillic acid/5-HIAA ratio, 3-methoxy-4-hydroxyphenylglycol (MHPG) levels and in cerebellum with 3,4-dihydroxyphenylacetic acid (DOPAC)/dopamine ratio, but no relationship between any neurotransmitter values and aggressive behavior. The same investigators found some correlation between neurotransmitter values and aggressive behavior in another paper, but in that study they compare only aggressive and non-aggressive subjects and did not include subjects with non-aggressive behavior as a separate group [21].

Differential involvement of the noradrenergic system is suggested by cell count in the locus coeruleus. Matthews et al [22] studied post-mortem brains of 46

individuals with a clinical diagnosis of dementia and 33 elderly normal control cases. The dementia individuals included 36 subjects with AD and 10 subjects with mixed dementia. All had pre-mortem longitudinal evaluation of their behavior using PBE scale. The investigators found that there was a strong correlation between the mean cell count at level A of the locus coeruleus and the presence of aggressive behavior during the illness, with lower cell counts being associated with an increased severity of aggressive behavior. There was no relationship between overactivity and cell count.

Discussion

The confusion regarding terminology of behavioral symptoms of dementia is not new and is perpetuated by the multitude of instruments used to evaluate these symptoms. A recent review evaluated 83 instruments developed to measure behavioral and psychological symptoms of dementia. [23]. This review is considering only those instruments that clearly differentiated between agitation and aggression, because only studies using these instruments could differentiate neurobiological substrates of these syndromes.

The first scales, that evaluated neurobiological substrate, were Cohen-Mansfield Agitation Inventory (CMAI) [24] in the United States and Present Behavioral Evaluation (PBE) [6] in the United Kingdom. Both of these scales differentiated agitation and aggression, although CMAI called physical and verbal aggressive behavior "agitation". Neither of these scales included psychiatric syndromes and this omission was corrected by development of the Neuropsychiatric Inventory (NPI) [25] that included not only behavioral but also psychiatric syndromes . However, there was a problem with this scale because one of the domains of the scale, Agitation/Aggression, combined in its name both of these syndromes, while it measured only reactive aggression resulting from rejection of care. Non-aggressive behavior, that was considered agitation in other scales was evaluated mostly by the domain Aberrant Motor Behavior.

Several efforts were made to simplify the response structure of NPI but they usually resulted in emphasizing psychiatric conditions instead of differentiating behavioral symptoms [26]. For instance, the Cache county study identified only three clusters: an affective syndrome, a psychotic syndrome and other neuropsychiatric disturbance [27]. The most recent factor analysis of NPI identified four subsyndromes: Hyperactivity, Psychosis, Affective, and Apathy. However, Aberrant Motor Behavior was included in three of these subsyndromes depending on the type of dementia [28]. More recently, NPI-C Research Group [29] designed new version of NPI that includes expanded domains, more items, and a clinician-rating methodology. This version separated Agitation and Aggression into two domains. Unfortunately, the probing question for agitation remained the same as in the original NPI "Is (S) hard to handle or uncooperative or resistive to care?" and thus this domain evaluates presence or absence of rejection of care which has nothing to do with agitation.

Despite this acknowledgement that agitation and aggression are two separate syndromes, a group of experts, convened by the International Psychogeriatric Association (IPA), developed provisional consensus stating that agitation is manifested by excessive motor activity, verbal aggression, or physical aggression [3]. Separation of agitation and aggression is complicated by the fact that both of these syndromes can occur in the same person [4]. However, they may not occur at same time, and this fact is not captured by the current scales relying in proxy reports, because these reports usually concern behaviors occurring during the past few weeks. It is hoped that evidence of differences in neurobiological substrates between agitation and aggression, presented in this paper, will be taken into consideration for possible revision of agitation definition.

Distinction between agitation and aggression is important for both non-pharmacological and pharmacological management of behavioral symptoms of dementia. Non-pharmacological strategies used for treatment of agitation need to concentrate on providing meaningful activities because agitation is often caused by boredom of persons with dementia [30]. In contrast, aggression is in most cases reactive aggression elicited by rejection of care. Therefore, its management should concentrate on improving communication and on changing care strategies to prevent escalation of rejection of care into combative behavior and reactive aggression [31]. Although drug studies were not specifically designed to evaluate effects on specific syndromes, there is some indication that medications

affect differentially agitation and aggression. Antipsychotics seems to be more effective in treatment of aggression [32] and risperidone is actually indicated for treatment of " persistent aggression in patients with moderate to severe Alzheimer's dementia" by the European Medicines Agency 33. In contrast, donepezil was found to improve only non-aggressive behaviors [34].

There is a danger that a medication may be developed and approved by the FDA with indication of agitation without recognizing the difference between agitation and aggression. It is important to realize that Minimum Data Set 3.0 does not contain the term agitation. It is distinguishing behavioral symptoms, according to the involvement of others, into behaviors directed towards others and behaviors not directed towards others. Aggression by definition involves others, while damaging equipment may be just an escalation of agitation (e.g., damaging a chair by restlessness), not directed toward others and not real aggression. Providers of care for persons with dementia need a clear connection between their evaluations and research results, and a confusing concept of agitation that includes aggression is not going to help the in providing appropriate care for persons with dementia who exhibit behavioral symptoms.

There are some limitations of this study. The main one is that there is not enough information available to construct a mechanism underlying neurobiological mechanisms related to agitation and aggression. Therefore, this paper is limited to pointing out that the neurobiological indices are differentiating these two syndromes. The second limitation is the use of results obtained with scales that rely on proxy reports. These scales do not provide information about the context in which these behaviors occurred. Thus, the same person may be considered to exhibit both agitation and aggression, but these behaviors may occur in different times and different contexts. However, despite these limitations, data presented in this review indicate that agitation and aggression should be considered as two independent syndromes. The third limitation is that subjects involved in these studies had several causes of dementia. However, large-scale studies showed no difference in the prevalence of neuropsychiatric behaviors between Alzheimer's disease and non-Alzheimer's disease dementias [35] and another study concluded that neuropsychiatric subsyndromes are consistent across dementia subtypes, age and gender [28]. Although the reviewed studies do not provide enough information about neurobiological changes in specific dementia subtypes, it is possible to suggest that agitation and aggression are two different syndromes in all subjects with dementia.

Conflict of Interest & Declaration

None

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