

SYMPTOMS AND SIGNS IN DEMENTIA: SYNERGY AND ANTAGONISM

Janice E. Graham, Arnold B. Mitnitski, Alexander J. Mogilner, Denis Gauvreau,
and Kenneth Rockwood

Abstract

This paper addresses the synergy and antagonism between symptoms and signs among 2914 elderly Canadians diagnosed in 15 categories, including no cognitive impairment, cognitive impairment but no dementia, mild, moderate and severe forms of Alzheimer's disease and vascular dementia, 4 subtypes of possible Alzheimer's disease, Parkinson's dementia, unspecified other dementias and unclassified dementias.

Attention is paid to the *relationships* between symptoms and signs rather than conventional analyses which assume independent signs. We demonstrate that dementia progression and specific aetiologies have characteristic patterns of decline and destruction from the strong synergy that exists between symptoms and signs among the population with no cognitive impairment. These findings have potential implications for the incorporation of new diagnostic criteria into existing databases.

The growth of interest in cognitive impairment has generated new approaches to dementia and an appreciation of the central importance of heterogeneity. The syndromic diagnosis (i.e. the definition of dementia) has been revised both in DSM-IV [1], and in ICD-10 [2]. An appreciation of previously unrecognized causes of dementia, such as the newly proposed criteria for frontotemporal dementia [3] and for Lewy body dementia [4], has coincided with substantial changes in the way in which more established causes of dementia are being defined. There has been a major change in the approach to vascular causes of dementia [5-9]. Even Alzheimer's disease [10] is encountering a serious challenge to diagnostic criteria as a result of improved understanding of the existence of definable subgroups [11-13]. This change in thinking about dementia has important consequences for clinical and public health practice, and for epidemiological study.

Once the syndromic diagnosis has been established, the goal for the diagnostician is to identify the cause of the dementia. In the absence of readily available biological markers, this depends on the clinical symptoms and signs. The overlap of configurations of symptoms and signs, compounded by comorbidity, represent key challenges to the aetiological diagnosis of dementia. In clinical practice the presence of one sign may not necessarily sound a clinical alarm. Rather, the emergence of certain *combinations of symptoms and signs* indicates characteristic disorder. Clinicians meet this challenge by recognizing patterns of symptoms and signs.

Any formal analysis of the differential diagnosis must therefore examine not just the occurrence of symptoms and signs, but the relationships between them. Among relationships, it is important to distinguish between *synergy*, i.e.; significant occurrence of one sign with another, and *antagonism*, i.e; signs in mutual distraction with each other, associated with aetiology and severity of dementia. We adopt these terms from epidemiology [14], where synergy is a situation in which the combined effect of two or more factors is greater than the sum of their solitary effects. In turn, antagonism reflects the situation in which the combined effect of two or more factors is smaller than the solitary effect of any one of the factors. We hypothesize that these coordinations (and their emergence, existence and disappearance) are important characteristics of the disease which will assist in a careful definition of cases [15]. We report patterns of synergistic and antagonistic relationships in disease expression in dementia.

Methods

Clinical Assessment Symptoms and Signs

The Canadian Study of Health and Aging (CSHA) database represents a national cross-sectional, representative sample of Canadians aged 65 and over. The study methods and clinical examination are described elsewhere [16,17]. Clinical assessment was performed on 2914 elderly Canadians, including 921 people with no cognitive impairment (NCI), 861 with some cognitive impairment but not dementia (CIND) and 1132 people with dementia. ICD-10 was used to evaluate severity. The clinical assessment included a neurological exam which explored signs relevant to degenerative and vascular dementias, a physical exam of symptoms and signs relevant to systemic conditions that could cause chronic encephalopathy, a medical history and an informant interview. In total, over 400 symptoms and signs were available as candidate variables.

Analysis

With over 400 variables to choose from, it was not our goal to explain all possible relationships. Instead, we selected 56 variables on the basis of their suspected clinical relevance. From these, we identified 19 symptoms and signs from our initial analysis which showed variance across the diagnostic categories (see Appendix 1). Probabilities (frequencies) and variances were calculated for the symptoms and signs across fifteen diagnostic categories in all 2914 cases.

If $p_i(X)$ is the probability of a sign X in the i-th diagnostic category, estimated as the frequency of occurrences of this sign in the i-th category, $i=1\dots n$, where n is the number of diagnostic categories, and $p_i(X|Y)$ is the *conditional* probability of sign X given the occurrence of sign Y, estimated as the number of cases within a diagnostic category where both X and Y occur simultaneously, divided by the number of cases with sign Y, the null hypothesis is determined by $p_i(X) - p_i(X|Y)=0$. If there is no significant difference between these two probabilities ($p_i(X)$ and $p_i(X|Y)$), X and Y are independent, i.e., the presence of Y does not effect the probability of X. Alternatively, we can say X and Y are dependent; a connection exists between the signs if $p_i(X) - p_i(X|Y)\dots 0$. To test the null hypothesis we used the Student T test:

$$t = \frac{p_i(X) - p_i(X|Y)}{\sqrt{p_i(X)(1 - p_i(X))/N_i}}$$

where N is the number of cases in the i-th diagnostic category with sign X [18]. The 95% significance level was used for testing the null hypothesis ($p<.05$). If the null hypothesis is rejected, we introduce the ratio $c_i(X,Y) = p_i(X|Y) / p_i(X)$ as an index of coordination (measure of synergy if index is greater than 1 and of antagonism if index is less than 1), between signs X and Y for the i-th category. This identifies how many more times the probability increases with the occurrence of X given Y, when compared to the random occurrence of X.

Another measure of dependence can be derived by taking the logarithm of this ratio: $\log(c_i(X,Y))$. A positive log value demonstrates synergy (X “attracts” Y); a negative log shows antagonism (X “distracts” Y); and a log of 0 shows the signs are independent.

Results

The polyhedrons in Figure 1 illustrate the connections between the signs analysed for the diagnostic categories no cognitive impairment (NCI), severe Alzheimer's disease, severe vascular dementia, and Parkinson's dementia. Solid lines represent synergy and dashed lines represent antagonism. The group No Cognitive Impairment shows many coordinations. This synergy decreases in the severe dementia groups. Intermediate pictures appear for mild and moderate forms. By way of a more detailed example, Figure 2 illustrates the strong coordination which exists between four neurological signs (facial bradykinesia, limb bradykinesia, limb tone and neck tone) among the NCI group. This is much weaker in the severe Alzheimer's disease group. The values of our synergy index $c_i(X,Y)$ show significant reduction (by more than 10 times) in the severe Alzheimer's disease group compared to the NCI group.

Because we had different numbers of cases in our diagnostic categories, we created an independent scale index, a ratio (C_i) which is independent of the group size. The value of this index is calculated by the number of significant connections (synergies) divided by the square root of the diagnostic sample size. It is shown to characterize the particular aetiological category (Table 1).

Another index which characterizes the aetiology may be defined as the maximum value of the coordination index. This maximum can be denoted as $M_i = \max_{\{X,Y\}} [c_i(X|Y)]$.

Table 1 shows that the maximum synergy value of 56 for the NCI group is dramatically reduced to 3 in the severe Alzheimer's diagnostic group.

The selected 19 signs does not exhaust the possible synergistic relations. Table 2, for example, illustrates the synergy existing between 2 additional signs, measures of activities of daily living (ADL) and independent activities of daily living (IADL) [19], which declines as the groups represented encounter greater degrees of cognitive impairment.

Discussion

We investigated relationships within a reduced set of symptoms and signs in the CSHA database and found two important results. The first is that distinct patterns exist between the symptoms and signs for different causes of dementia. The second is that, across all dementia types, there are fewer relationships as the dementia becomes more severe. The patterns of relationships are complex, and in consequence we have relied on the concepts of synergy and antagonism to help clarify these patterns.

We now address three questions: what caveats must be understood; what might these patterns mean in clinical terms, and; what more must be done? As this is a secondary analysis, we do not have available all the data which we would like. For example, we do not know about the duration of the individual signs. On the other hand, we do know about staging, which can serve as a useful surrogate for duration. We also have the advantage of a very large database of careful clinical observations, including staging markers, based on a standardized protocol. Data on duration would require a degree of longitudinal observation which might exceed that of usual clinical care, and which would hardly be feasible for population-based studies.

The meaning of these patterns, though necessarily speculative, is intriguing. The patterns discerned by the mathematical modelling reflect well the underlying clinical patterns. For example, in severe Alzheimer's disease, increased limb tone is synergistically associated with (i.e. makes more likely) increased neck tone, agitation, and decreased muscle bulk. The modelling also identifies other relationships which allow for hypothesis generation: for example, in severe Alzheimer's disease, there are many relationships between vascular risk factors such as arterial hypertension and stroke and features of disease expression such as mood and muscle bulk and tone. Given recent data relating vascular risk factors to all causes of cognitive impairment in old age, there is merit in more carefully exploring the role of vascular risk factors in disease expression in dementia [20-23].

Of considerable interest is the strong relationship between the number and strength of clinical signs in the no cognitive impairment category. This density of connections seems to reflect the plural feedbacks which are necessary for reliable functioning of the healthy organism [24]. In contrast, the dementia groups show weakened associations (distractions) between the signs. The severe stages of dementia are mirrored by dramatic reductions in these connections. In support of this relationship between the types and density of connections and severity of dementia, we have observed that in mild and moderate dementia there is an intermediate picture between severe forms of dementia and no cognitive impairment. The pattern therefore suggests loss of information as dementia progresses.

The density of connections can be numerically captured in the value of the index c_i , which shows how many times the probability of one sign changes, given the second sign, when compared to the independent occurrence of the first. As expected, the coordination index declines as the dementia becomes more severe. Even though the same signs may occur more commonly, as cognitive functioning declines, synergies weaken.

While the coordination index, as developed here, provides insights about disease expression for diagnostic groups it also provides the fundamental concepts for classifying individual cases. The coordination index can be used to derive insights into individual cases by an algorithmic approach reported separately [25]

Our data also suggest that the discrete patterns seen in different dementia causes can be discerned on the basis of a comparatively few signs. Considerable redundancy is manifest between connections and coordinations of the observed signs and symptoms. A linguistic analogy might serve to illustrate this: one can often understand the meaning although speech may be grammatically incorrect. Different dialects may

have elements which are mutually interpretable or distinct, but they also contain blurred areas where meaning is compromised. There is sufficient redundancy in language however to still obtain the essential meaning. It is therefore at least theoretically possible to dramatically reduce the number of signs necessary for differential diagnosis without losing essential information.

Finally, this analysis introduces the possibility that new criteria can be adapted into existing databases by examining conditional probabilities of the new interpretations of signs. For example, the diagnostic criteria of Lewy body disease include only one new sign (neuroleptic sensitivity syndrome) [4]. The other criteria arise from a reordering of symptoms and signs already routinely assessed in dementia; i.e. they form an alternate pattern. Techniques such as those proposed in this paper provide a possible method by which to "update" datasets such as the CSHA when new criteria emerge, through the analysis of alternate patterns of existing signs.

Acknowledgments

The study was supported by the Camp Hill Medical Centre Research Foundation, Halifax, Nova Scotia. The data reported in this article were collected as part of the Canadian Study of Health and Aging. This was funded by the Seniors Independence Research Program, administered by the National Health Research and Development Program (NHRDP) of Health and Welfare Canada. The study was also supported in part by NHRDP through a National Health Scholar award to Dr. Rockwood, and by Projet IMAGE, Montréal through its doctoral support of J.Graham.

References

1. American Psychiatric Association: Diagnostic and statistical manual of mental disorders, fourth edition, Washington, D.C.: American Psychiatric Association, 1994.
2. World Health Organization: The ICD-10 Classification of Mental and Behavioural Disorders: diagnostic criteria for research. Geneva: World Health Organization, 1993.
3. The Lund and Manchester Groups: Clinical and neuropathological criteria for frontotemporal dementia: consensus statement. *J Neurol Neurosurg Psychiatry* 1994;57:416-418.
4. McKeith I, Perry RH, Fairbairn AF, Jabeen S, Perry EK: Operational criteria for senile dementia of Lewy body type. *Psychological Med* 1992;22:911-922.
5. Román GC, Tatemichi TK, Erkinjuntii T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo J-M, Brun A, Hofman A, Moody DM, O'Brien MD, Yamaguchi T, Grafman J, Drayer BP, Bennett DA, Fisher M, Ogata J, Kokmen E, Bermejo F, Wolf PA, Gorelick PB, Bick KL, Pajeau AK, Bell MA, DeCarli C, Culebras A, Korczyn AD, Bogousslavsky J, Hartmann A, Scheinberg: Vascular dementia: diagnostic criteria for research studies. *Neurology* 1993; 43:250-260.
6. Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R: Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. *Neurology* 1992; 42:473-480.
7. Rockwood K, Parhad I, Hachinski V, Erkinjuntti T, Rewcastle B, Kertesz A, Eastwood MR, Phillips S: Diagnosis of vascular dementia: Consortium of Canadian Centres for Clinical Cognitive Research Concensus Statement. *Can J Neurol Sci* 1994;21:358-364.
8. Hachinski V: Preventable senility: a call for action against the vascular dementias. *Lancet* 1992;340:645-648.
9. Hachinski V: Vascular dementia: a radical redefinition. *Dementia* 1994;5:130-132.
10. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939-944.
11. Erkinjuntti T, Hachinski VC, Sulkava R: Alzheimer disease and vascular dementia. In *Dementia: Presentations, Differential Diagnosis, and Nosology*, edited by VOB Emery and TE Oxman. Baltimore: Johns Hopkins University Press, 1994. Pp. 208-231.
12. Blennow K, Wallin A, Gottfries CG: Clinical subgroups of Alzheimer disease. In *Dementia: Presentations, Differential Diagnosis, and Nosology*, edited by VOB Emery and TE Oxman. Baltimore: Johns Hopkins University Press, 1994. Pp. 95-107.
13. Emery VOB, Oxman TE: The spectra of dementia. In *Dementia: Presentations, Differential Diagnosis, and Nosology*, edited by VOB Emery and TE Oxman. Baltimore: Johns Hopkins University Press, 1994. Pp. 384-407.
14. Last JM: A dictionary of epidemiology. 2nd ed. New York, Oxford University Press, 1988.
15. Brayne C, Day N, Gill C: Methodologic issues in screening for dementia. *Neuroepidemiology* 1992;11(Suppl 1):88-93.
16. Canadian Study of Health and Aging Working Group: Canadian Study of Health and Aging: study methods and prevalence of dementia. *Can Med Assoc J* 1994;150:899-913.
17. Graham JE, Rockwood K, Beattie BL, McDowell I, Eastwood R, Gauthier S: Standardization of the diagnosis of dementia in the Canadian Study of Health and Aging. *Neuroepidemiology* 1996; In press.
18. Afifi A. A., Azen S.P: Statistical analysis: a computer oriented approach. New York:Academic Press, 1979.
19. Fillenbaum GG, Smyer MA: The development, validity, and reliability of the OARS multidimensional functional assessment questionnaire. *Journal of Gerontology* 1981; 36:428-434.
20. Launer LJ, Masaki K, Petrovitch H et al: The association between midlife blood pressure levels and late-life cognitive function. *JAMA* 1995;274:1846-1851.
21. White L: Is silent cerebrovascular disease an important cause of late-life cognitive decline? *J Am*

- Geriatric Soc 1996;44:328-329.
22. Gale CR, Martyn CN, Cooper C: Cognitive impairment and mortality in a cohort of elderly people. *Br Med J* 1996; 312:608-611
 23. Ferrucci L, Guralnik JM, Salive ME, Pahor M, Corti M-C, Baroni A, Havlik RJ: Cognitive impairment and risk of stroke in the older population. *J Am Geriatric Soc* 1996 44:237-241.
 24. Witten M: Reliability theoretic methods and aging: critical elements, hierarchies and longevity - interpreting survival curves. In, Woodhead AD, Blackett AD, Hollaender A (eds): *Molecular Biology of Aging*, Plenum Pr, New York, 1985:345-361.
 25. Graham JE, Mitnitski AB, Mogilner AJ, Gauvreau D, Rockwood K: An algorithmic approach to the differential diagnosis of dementia. Submitted to *Dementia*, April 1996.

Table 1. Values of the indices characterizing four diagnostic categories

	No Cognitive Impairment	Severe Alzheimer's	Parkinson's Dementia	Severe Vascular
Independent scale index (C_i)	3.0	1.8	0.96	0.6
Maximum value of synergy index (M_i)	55.58	5.77	3.02	3.34

Table 2. Decline in synergy index c_i (ADL, IADL) with stage of cognitive impairment

Synergy Index	NCI	CIND	Mild AD	Moderate AD	Severe AD
synergy(c_i)	7.42	2.64	1.84	1.17	0.99

Appendix 1. List of symptoms and signs in the present analysis

Clinical history: arterial hypertension [A], episodes of agitation [G], stroke [J], memory [K], mood (e.g. anxiety, sadness) [L]; *CAMDEX (informant interview):* clouding/delirium [E]; *Neurological Examination:* facial bradykinesia [B], limb bradykinesia [C], limb tone [P], neck tone [Q], muscle bulk [D], strength [O], posture [M], limb coordination [F], gait pattern [I], resting tremor [N], action tremor [R], voice [S], focal signs [H].

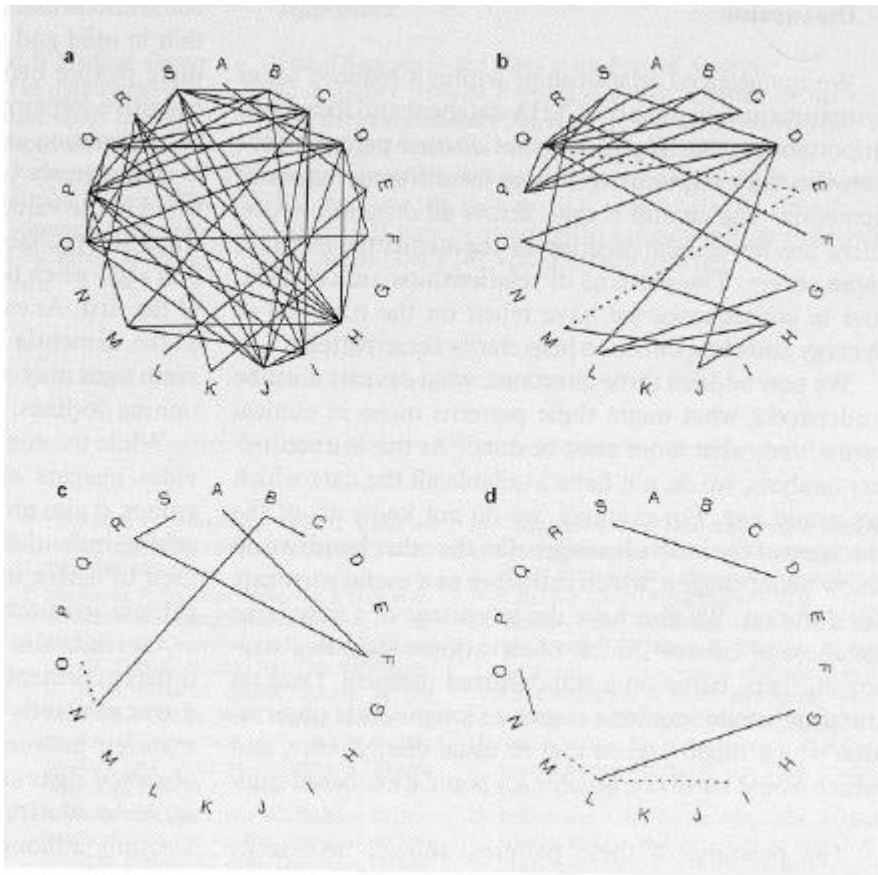


Figure 1. Inter-sign connections for a sample of NCI (**a**; n=199); severe Alzheimer's disease (**b**; n=199); severe vascular dementia (**c**; n=72), and Parkinson's dementia (**d**; n=27). Symptoms and signs are represented by letters A-S. Significant connections ($p < 0,05$) are represented by solid (synergy) or dashed (antagonism) lines

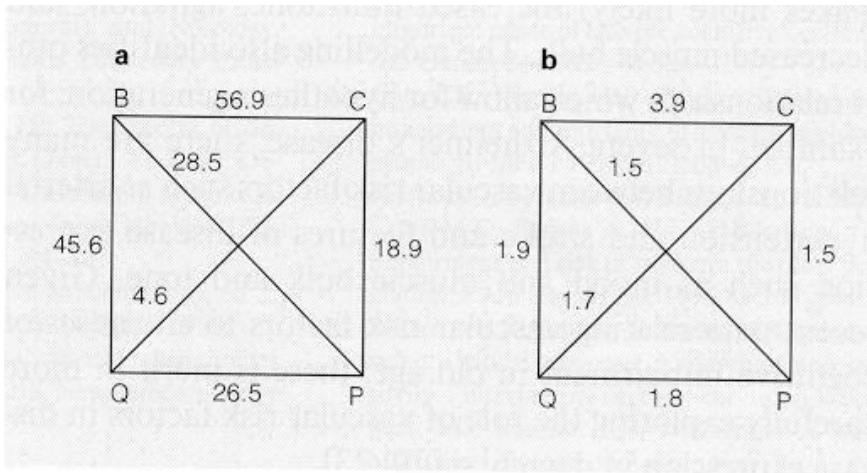


Figure 2. Inter-sign connections for B,C,P,Q in an equivalent sample of NCI (a; n=199) and severe Alzheimer's disease (b; n=19). The numbers represent the value of the ratio $c_i(X,Y)=p(X|Y)/p(Y)$.