Apathy: Why Care?

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This review presents data showing that apathy is common across a number of disorders. Apathy is not only common, but is also associated with significant problems: reduced functional level, decreased response to treatment, poor illness outcome, caregiver distress, and chronicity. Preliminary evidence of treatment efficacy exists for dopaminergic drugs and for amphetamines. Strong evidence of efficacy exists for acetylcholinesterase inhibitors in Alzheimer's disease, and for atypical antipsychotics in schizophrenia. Frontal-subcortical system(s) dysfunction is implicated in the causation of apathy; apathy subtypes based on the various frontal-subcortical loops may thus exist. Further research involving diagnosis, pathophysiology, and treatment is suggested.

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The syndrome of apathy has received considerable research attention over the last 10 to 15 years, and is receiving increasing recognition by clinicians working with neuropsychiatric populations. Apathy appears to be common in many disorders of the brain, is associated with a number of adverse outcomes, and is potentially treatable. This paper reviews the prevalence of apathy, its outcome correlates, its treatment, and its causation. The paper begins with a review of definitions and assessment tools, and concludes with suggestions for further research. The goal of the paper is to increase the recognition of apathy as an important clinical and research problem (i.e., we all need to "care" about apathy).

DEFINITION, CLINICAL FEATURES, AND ASSESSMENT TOOLS

The term "apathy" is generally defined in English language dictionaries as a lack of interest or emotion. Terms which are related to apathy, or which may be synony-

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mous with apathy, include abulia (perhaps reflecting severe apathy), amotivational states, and negative symptoms (e.g., as frequently used in the schizophrenia literature). Clinically, the authors have had apathy described (e.g., by patients and families) as "the get up and go that got up and went," or "the spark is missing." Marin,[1] whose work served as a major stimulus to research interest in apathy, felt that apathy embraces a number of psychological features, and defined apathy as being, at its core, a lack of motivation. Marin[2] distinguished between apathy as a symptom (i.e., of mood disorder, altered level of consciousness, or cognitive impairment), and apathy as a syndrome of acquired changes in mood (affect), behavior, and cognition not due to mood disorder, altered level of consciousness or cognitive impairment. Marin proposed DSM-like criteria that have not been widely accepted, but which may yet provide a basis for the development of a criteria set for the DSM.

Stuss et al.[3] noted that the definition and assessment of motivation is problematic, and suggested that apathy be defined as an absence of responsiveness to stimuli, with the requirement that this lack of responsiveness be demonstrated by a lack of self-initiated action. Hence initiation is central to the definition of apathy of Stuss et al. The self-initiated response may be affective, behavioral or cognitive in nature. Stuss et al.[3] also propose that apathy may in fact represent a number of related but separable states, depending on the neural substrate, and/or the behavioral response, involved. This concept will be further discussed later.

Most of the clinical research to date has "defined" apathy on the basis of scores on various assessment tools. The development of these measures has greatly facilitated and promoted research into apathy. The most commonly used measures to date include the Apathy Evaluation Scale,[4] the Neuropsychiatric Inventory,[5] a brief version of the Apathy Evaluation Scale called the Apathy Scale, and a number of measures used primarily in schizophrenia research. These scales are generally reliable, valid, and feasible for use in both research and the clinical setting. The Neuropsychiatric Inventory has the advantage of assessing other realms of behavior which are commonly altered in neuropsychiatric disorders. However, it is not clear what the appropriate cutoff score is for the presence of the apathy syndrome, nor is it always clear from the research using the Neuropsychiatric Inventory what cutoff score has been used. For example, if apathetic behavior is assessed by the Neuropsychiatric Inventory as being frequent, but mild, would this be considered clinically relevant apathy? Further evaluation of the apathy subscale of the Neuropsychiatric Inventory, as might be done, for example, with receiver-operating curve analysis with an appropriate clinical gold standard, might help improve clinical confidence when using this subscale of the Neuropsychiatric Inventory. There is as of yet no consensus as to what the appropriate clinical gold standard should be, suggesting that such a consensus is much needed.

PREVALENCE

The following review summarizes data derived from an extensive literature search of MEDLINE using a broad number of search strategies (e.g., key words, text words, citation searches of important authors) and terms (e.g., apathy, motivation, initiation, negative symptoms, abulia, amotivation, etc.), as well as follow-up on references identified in papers found. The review proceeds by considering diagnostic categories and related groupings (e.g., Huntington's disease and Parkinson's disease, amongst others, in the subcortical disorders section). Data are presented as averages across studies (to facilitate discussion and to help assimilate findings for the reader), with the recognition that averaging data across studies raises concern with statistical validity given that studies have employed different methodologies. To address this the paper will also present the range of prevalence data found.

There are six studies[7–12] which use the Neuropsychiatric Inventory to assess the point prevalence of apathy in outpatients with Alzheimer's disease (AD). One hundred seventy of 261 AD outpatients studied were identified as having apathy on the Neuropsychiatric Inventory, for an average point prevalence of 65.1%. The lowest prevalence rate found was 55%[8] and the highest was 80.6%.[10] Studies using the Apathy Evaluation Scale,[13] the Apathy Scale,[14] the Blessed Dementia Scale,[15] and other instruments[16,17] combine to provide a point prevalence of 58.5% (432/738) in this population. The lowest rate found was 37.0%,[14] and the highest was 86.4%.[13] It appears that estimates of the prevalence of apathy using the Neuropsychiatric Inventory are comparable to estimates of apathy prevalence when compared with other measures collectively. Combining all of the data for Alzheimer's outpatients provides a point prevalence of 60.3% (602/999). Clearly apathy appears

to be very common in Alzheimer's outpatients. While not providing quantitative data, additional studies support this finding. Apathy has been found to be more common in AD outpatients than in normal comparison subjects.[18,19] However, other studies suggest that apathy may be less common in AD outpatients than it is in Huntington's disease[20] or vascular dementia.[21]

Apathy appears to be less common in AD when the study sample is derived from the community,[22,23] with a combined community point prevalence of 32.8% (84/256). The lowest rate was 29%[22] and the highest was 52.4%.[23] This data suggests that apathy is associated with the decision to seek outpatient care, either because apathy is perceived as being a problem in its own right, or because of its associated outcomes. There are two studies in which the source of subjects was not identified,[24,25] and these provided a point prevalence of 60.0% (30/50). Combining these studies with the outpatient totals provides an overall averaged point prevalence of apathy in AD of 55.5% (752/1355). It may be that the overall rates for AD are in fact higher, as apathy in long-term care settings has not been well assessed.

Apathy has also been studied in traumatic brain injury (TBI), with three studies employing the Apathy Evaluation Scale[26–28] and two employing other scales.[29,30] In total 304 subjects have been assessed; 142 were found to be apathetic, for a point prevalence of 46.7%. However, one study[29] assessed only children and adolescents. In this group, apathy was found to occur at a rate of only 13.8%. In the studies which assessed adults[26–28,30] the point prevalence was 61.4% (129/210). The lowest prevalence rate found in the TBI studies was 46.4%,[28] and the highest was 71.1%.[26] The average rate of 61.4% is very similar to that found in AD, suggesting that different brain pathologies, which involve the cortex, may cause apathy at similar rates.

This trend seems to be continued in the population who have suffered a focal frontal lesion.[12,31–33] Forty-one of 68 subjects assessed have been felt to have apathy on a variety of measures (including clinical observation), yielding an average point prevalence of 60.3%. The highest rate found was 89.3%[12] and the lowest was 12.5%.[31] Some of this data is also relevant regarding brain and behavior relationships in apathy. For example, 12.5% of patients with medial frontal lesions developed apathy, while 62.5% of patients with lateral frontal lesions were apathetic in one study using the Present State Examination in a relatively small group of 16 subjects.[31] In contrast, another study[33] showed that apathy was present in five (71.4%) of seven patients with a bilateral ventromedial lesion(s), but in only three (21.4%) of 14 patients with a nonmedial but still frontal lesion. Clearly frontal lesions are associated with apathy, and indeed another study suggests that apathy in this group is more common than apathy in major depression, bipolar affective disorder, and normal comparison subjects.[34] However, there is some conflicting data from these studies as to the frontal area of most significance to apathy.

Individuals with lesions or illnesses involving the basal ganglia seem to show a lower averaged point prevalence than has been found in the disorders with cortical involvement described above. Twelve studies have assessed rates of apathy in these populations on a variety of scales (most often the Neuropsychiatric Inventory). These data include subjects with focal lesions of the septal gray matter,[35] bilateral globus pallidum,[36] and caudate/putamen/globus pallidum,[37–39] as well as Parkinson's disease,[6,12,23,40,41] Huntington's disease,[12,42] and progressive supranuclear palsy.[12,40,43] Excluding the three case reports[35–37] provides a total of 589 subjects[6,12,23,38–43] assessed, with 239 diagnosed with apathy. The pooled point prevalence of 40.6% is roughly two-thirds that seen in the cortical involvement disorders, where rates approximating 60% have generally been seen. The range of rates is from a low of 12.9%[38] to a high of 90.0%.[12] Interestingly, in corticobasal degeneration,[43] which involves both subcortical and cortical structures, the rate seen in basal ganglia disorders was most closely approximated (40.0% of 15 subjects had apathy). Apathy may also be caused by lesions of the inferior genu of the internal capsule.[44]

While a point prevalence cannot be estimated (given a combined sample size of only 26) in patients with lesions of the thalamus, it has frequently been reported.[45–51]

Apathy has been reported in other populations at fairly high rates. Two studies of vascular dementia[8,22] yield a rate of 33.8% in a combined sample of 145 subjects. Four studies[25,28,52,53] of a combined 190 patients poststroke yield an average point prevalence of 34.7% (range = 22.5%[53] to 56.7%[28]). An extraordinarily high rate of 78.6% was found in 14 subjects postanoxic brain injury in one of these studies.[28] There was a slightly higher rate of apathy in right-hemisphere strokes (31.8%) than in strokes involving the left hemisphere (22.2%) in one study.[25] A literature review identified apathy in eight (22.2%) of 36 cases of dementia with Lewy bodies[54] while apathy was reported as being common

in a study of 120 patients with dementia with Lewy bodies.[55] Two studies of HIV-infected outpatients[56,57] yield an averaged point prevalence of 29.8% (54/181). Another study[58] reported that nearly 50% of 65 HIV outpatients studied had apathy. Apathy has been reported in 20.5% of 44 patients with multiple sclerosis[59] and in 53.3% of 30 patients with major depression.[25] It is reportedly[60] more common in myotonic dystrophy than in Charcot-Marie-Tooth disease (suggesting to the authors that the nervous system involvement seen in myotonic dystrophy is at least part of, but perhaps not all of, the cause of apathy). Finally the highest prevalence found to date is not in any one diagnostic category, but rather in nursing home residents, suggesting that either severity of illness(es) plays a role in producing apathy, or that the context of the chronic care setting (e.g., possible lack of stimulation) is also contributing. 84.1% of 69 nursing home residents were found to be apathetic as reported by the Neuropsychiatric Inventory.[61]

In summary of the prevalence data, apathy appears to be very common in a number of disorders of the brain, with disorders which directly involve the cortex showing averaged point prevalences of approximately 60%, and disorders of subcortical structures developing apathy at roughly a 40% rate. Again it must be noted that averaged prevalence rates obtained from data employing different methodologies must be interpreted with caution, but it would appear that apathy may be slightly more common in cortical than in subcortical disorders. It would also appear from the prevalence data that limbic-frontal-subcortical circuits are potentially implicated in the pathophysiology of apathy in these disorders. Further evidence in support of this hypothesis will be reviewed later in this paper. The prevalence data also begin to suggest that the Neuropsychiatric Inventory is measuring the same phenomenon as other apathy scales, given the similarity in group rates reported. However, direct comparisons between the various measures are still required. Apathy is common, but clinical relevance will be established not only by prevalence, but by findings which suggest that apathy may contribute to other adverse outcomes. We now turn to a review of the associated outcomes of apathy.

ASSOCIATED OUTCOMES

Apathy has been associated with a number of adverse outcomes. However, it is not yet clear that apathy *causes* these adverse outcomes. Of course in any association, A (here used to denote apathy) may cause B, or B cause A, or some third factor, C, may cause both A and B and be responsible for the apparent association between A and B. Brain dysfunction, in brain regions to be discussed more fully later, may be the hidden third factor (C) underlying some of the associations described below. It may also be the case that some of the adverse outcomes are reciprocally contributing to the degree of apathy (B causing A). For example, an individual who suffers loss of function, such as role loss (particularly when there is no hope of resuming the role) postneurological insult might well be expected to develop a degree of apathy due to the combination of loss and hopelessness. None the less, it is plausible that apathy might well contribute significantly to the following adverse outcomes.

Four studies, all of which employed the Apathy Evaluation Scale or the Apathy Scale, have established an association between apathy and decreased functional level. Apathetic AD patients, with or without comorbid depression, were found to function lower in terms of their activities of daily living.[14] The Apathy Evaluation Scale was found to correlate ($R = -0.348$, $p<0.05$) with a measure of instrumental activities of daily living in AD.[13] In a stroke inpatient unit, apathetic and depressed patients were more functionally impaired than were apathetic patients alone.[53] However, apathetic patients who were not depressed ranked second in terms of degree of functional impairment, and were in turn more impaired than the depressed (but not apathetic) group and the group who were neither depressed nor apathetic. Finally, in a cohort derived from a geriatric inpatient rehabilitation unit (common diagnoses included stroke and hip fracture, etc.), apathy at admission was the second independent variable to enter a regression model predicting discharge level of function ($p<0.05$).[62]

Apathy also appears to be associated with distress in caregivers. In AD outpatients, caregiver distress correlated with Neuropsychiatric Inventory-rated apathy with an $r = 0.5$ ($p<0.001$).[9] In another study in this population, apathy was the most commonly complained of behavior by caregivers.[13] However, in TBI outpatients, apathy, while still commonly complained about by caregivers, ranked third as the most problematic behavior.[30] Interestingly, and perhaps self-evidently, apathy may not be of concern to the apathetic patient. In schizophrenia, patients were found to not be distressed by their apathy.[63] Self-awareness deficits in at least some apathy states are suggested by this finding. Studies ex-

amining the diagnostic, prognostic and treatment implications of comorbid apathy and lack of self-awareness may yield important results.

Apathy also appears to be associated with poor outcome of illness. In AD outpatients a faster rate of decline in cognitive function, as assessed by the Mini Mental State Examination (MMSE), was found in the apathetic versus nonapathetic group.[17] In major depression, apathy at baseline correlated inversely with depression outcome with an $r = -0.46$ ($p = 0.001$).[64]) In a study of late-life major depression, persistent apathy was associated with depression outcome.[65]

Apathy has also been associated with poor treatment response. In geriatric inpatients apathy correlated with lack of participation in rehabilitation with an $r = 0.372$ ($p < 0.05$).[62] In AD outpatients apathy was more common in those who did not show a behavioral response to donepezil.[66] In schizophrenia, apathy is more common in those who are not compliant with medication therapy.[67] Apathy also appears to interact with cognitive impairment in predicting response to social skills training in schizophrenia, as those who are both apathetic and cognitively impaired show the poorest response to this intervention.[68]

Finally, apathy appears to often be a chronic condition. In the only longitudinal data to date, apathy in AD was found to persist, and indeed worsen, over 33 months of follow-up.[69]

It would appear that apathy is not only common, but problematic as well. It has been associated with decreased functional level, caregiver (but possibly not patient) distress, poorer outcome of illness and poorer treatment response, and chronicity. While the direction of causality is not clear, and indeed may be multidirectional, it would appear that the treatment of apathy warrants consideration.

TREATMENT

Pharmacological interventions for apathy have included trials of dopaminergic agents, amphetamines, atypical antipsychotics and acetylcholinesterase inhibitors. Dopaminergic agents have received only preliminary study as a treatment for apathy. Bromocriptine has been studied(45,70–73) in a total of only 17 subjects (primarily TBI and poststroke), and there are no randomized controlled trials (RCTs). Doses of bromocriptine have ranged from 10–120 mg/day. Subjects have been felt to improve in terms of decreased apathy, and increased motivation, participation or spontaneity. Amantadine has been studied in a total of 14 apathetic subjects.[74–78] Only one was a RCT, and while the data were more rigorous (than open-label study data) and amantadine was found to consistently show positive results which impacted on the patient's functional abilities, the study was limited by an N of only one.[77] Doses have ranged from 300 to 900 mg/day. Similar changes to those seen with bromocriptine have been reported, and additionally some subjects have been observed to show increased function and decreased affective lability. Amantadine's effects on apathy have also been studied in subjects who were not selected on the basis of presence of apathy. In a crossover RCT, 29 fatigued subjects with multiple sclerosis[79] derived improvement in their perception of daytime energy levels with amantadine 100 mg. twice daily, but self-rated motivation was not felt to have improved. Treatment with amantadine 50–100 mg/day (for viral prophylaxis) in long-term care patients led to improved sociability, personal care and food intake in eight of 82 treated subjects.[80]

Methylphenidate and *d*-amphetamine, both widely used amphetamines, have been studied as a treatment for apathy in 225 subjects with multiple neurological diagnoses (R. Kant, personal communication, July 17, 1996).[1,71,81–85] Methylphenidate has had the most study to date. Again there are no RCTs. The dose range of methylphenidate employed in these studies is 5–30 mg/day (there is perhaps room to try higher doses as methylphenidate for other indications is used at doses up to 1 mg/day per kg of body weight). Subjects have been assessed on a wide variety of scales and using clinical observation, and are reported to have improved in terms of apathy, motivation, decreased negative symptoms, socialization, participation, hygiene, and psychic activation. A positron emission tomography (PET) study showing decreased basal ganglia activity with methylphenidate infusion in healthy volunteers[86] suggests that methylphenidate's mechanism of action may relate to alteration in the functioning of subcortical-cortical loops at the level of the basal ganglia.

The negative symptoms of schizophrenia strongly resemble apathetic affect and behavior. The treatment of the negative symptoms of schizophrenia with atypical antipsychotics (including risperidone, olanzapine and clozapine) has received considerable research attention. There are six RCTs with a total N of 3,182 subjects.[87–92] Five of these six studies showed improvement with

atypical antipsychotics in terms of decreased negative symptoms. One study[89] showed no benefit with olanzapine 5–15 mg/day for negative symptoms. There is a case report involving a subject who developed bipolar affective disorder following a left temporal stroke. This subject became more involved, and appetite improved, with risperidone 2 mg twice daily.[93]

Acetylcholinesterase inhibitors have been widely studied in AD for the indication of cognitive impairment. Subjects have not been selected on the basis of presence of apathy. A meta-analysis of RCTs[94] identified 2,218 subjects in whom apathy was felt to decrease with metrifonate versus placebo. Apathy was also found to decrease versus placebo with tacrine[95] and with donepezil;[96] however, another study did not show improvement in apathy with donepezil[66] despite a reasonably large sample size (N = 86). An open-label study of rivastigmine preliminarily showed benefit for apathy in 11 subjects with dementia with Lewy bodies.[97]

In summary of the treatment data, there is preliminary but methodologically limited evidence of possible efficacy for dopaminergic agents and amphetamines for apathy. There is solid RCT level evidence of efficacy for acetylcholinesterase inhibitors in AD, even though subjects have not yet been selected on the basis of the presence of apathy. Atypical antipsychotics reduce negative symptoms in schizophrenia. Further study of the role of acetylcholinesterase inhibitors for apathy in other disorders (e.g., dementia with Lewy bodies, TBI, etc.) is indicated and supported by the evidence to date. Randomized controlled trials of the efficacy of atypical antipsychotics in other psychotic populations should consider also evaluating apathy as an outcome. The neurotransmitter systems implicated by the treatment studies done to date include dopamine, acetylcholine, serotonin, and norepinephrine. Limbic-frontal-subcortical systems are again implicated by the treatment data. Additional evidence also exists to implicate these systems, and this evidence is now reviewed.

CAUSATION

Neuroimaging and Autopsy Studies

The anterior cingulate has been implicated in three studies to date. In single photon emission computed tomography (SPECT) studies of AD subjects, Neuropsychiatric Inventory-rated apathy correlated strongly and inversely with right anterior cingulate activity ($R = -0.61$, $p<0.005$)[7] or with bilateral reduction in cingulate activity.[24] At autopsy, AD subjects' Neuropsychiatric Inventory-rated apathy correlated with neurofibrillary tangle burden in the left anterior cingulate.[98]

Frontal regions are implicated by a number of studies. An apathetic patient postbilateral thalamic stroke showed reduced perfusion on SPECT in bilateral frontal regions.[47] Reduced regional cerebral blood flow in right dorsolateral prefrontal cortex and in left frontotemporal regions was demonstrated with xenon inhalation in apathetic stroke patients.[52] In a case report of a patient with postanterior communicating artery hemorrhage, increased perfusion in the right superior frontal region was observed (via SPECT) as apathy decreased with bromocriptine.[70] Similarly, bifrontal decreased perfusion was observed via SPECT in an apathetic patient after subcortical stroke.[71] Perfusion increased as apathy decreased with methylphenidate.

Subcortical regions are also implicated by neuroimaging studies. SPECT imaging of a single apathetic AD case revealed decreased perfusion in bilateral basal ganglia as well as in the dorsolateral prefrontal cortex.[99] Apathy was associated with computerized tomography (CT) lesions in the posterior limb of the internal capsule in 80 stroke subjects.[53] Apathy was also associated with lesions in subcortical structures, and in the right hemisphere, in 70 TBI subjects assessed by CT, magnetic resonance imaging (MRI), and EEG.[100]

Involvement of components of subcortical-frontal systems are implicated by the above findings, and further support for systemwide involvement is derived from the following two studies. Decreased perfusion on SPECT correlated with Neuropsychiatric Inventory-rated apathy in AD, with r values ranging from 0.36 to 0.45 for brain regions which included the anterior temporal regions, anterior cingulate, orbitofrontal cortex, dorsolateral prefrontal cortex, and the thalamus.[10] Similarly, in a case report of an apathetic patient after bilateral thalamic stroke,[46] apathy was associated with decreased activity (as demonstrated by SPECT scanning) in bilateral thalamus, caudate, and mesiofrontal regions.

Temporoparietal region involvement was implicated in a single study of AD employing SPECT.[101] In schizophrenia an association between negative symptoms and increased ventricle size was found.[102] This review also considered other research in schizophrenia which seemed to emphasize frontal system dysfunction in apathy on the basis of findings of reduced regional cerebral

blood flow during cognitive tasks in subjects with negative symptoms, and hypofrontal PET in negative symptom schizophrenia.[102] A negative finding occurred in patients with multiple sclerosis,[59] in whom apathy did not correlate with MRI-detected multiple sclerosis lesions.

Taken on the whole, the neuroimaging and autopsy studies appear to implicate subcortical-frontal circuits, involving in particular the anterior cingulate and the dorsolateral prefrontal cortex, in the pathophysiology of apathy.

Association With Cognitive Dysfunction

Eight studies[12,17,18,19,23,53,55,62] show an association between apathy and cognitive dysfunction as assessed by the MMSE in 649 combined subjects with a broad range of diagnoses. In the five studies reporting on correlations, the range of r values (apathy versus MMSE) has been between -0.4 and -0.81. One study[53] reported on group MMSE scores in apathetic (mean = 20.1) and nonapathetic (mean = 23.5) stroke patients ($p<0.0001$). However, there have been seven studies,[6–8,23,42,82,101] with a combined sample size of 334 subjects and a broad range of diagnoses, which have revealed a lack of association between apathy and the MMSE. It may be that the MMSE, which lacks sensitivity particularly for frontal system cognitive impairment, is not the ideal assessment tool for the establishment of causative relationships in apathy. Results from neuropsychological testing have yielded results consistently pointing towards frontal system cognitive dysfunction associated with apathy, and these are now reviewed.

A number of findings have been made in the AD population. Decreased performance was demonstrated on the Buschke-Selective Reminding Test (total and delayed), Boston Naming Test, Wisconsin Card Sorting Test, the Purdue Pegboard, and verbal fluency in apathetic AD subjects.[103] Similarly apathy correlated inversely (i.e., increased apathy was associated with poorer cognitive performance) and significantly with the Mattis Dementia Rating Scale, along with the initiation-perseveration and construction subscales of the Mattis Dementia Rating Scale, in AD patients.[20] Apathy has been associated with decreased insight in AD.[14] Increased apathy was associated with decreased novelty P_3 event-related potentials and with decreased attention to novel stimuli.[104] A similar study again showed this decrease in attention to novel and incongruous objects[105] while general measures of attention did not vary with apathy.

In TBI, apathy was again found to be associated with altered response to novel stimuli, as apathy correlated strongly ($r = -0.69$) with the "hits score" to novel stimuli.[106] Two studies involving TBI subjects show alterations in physiologic responsivity associated with apathy. Apathy correlated with heart rate during performance of the Raven's Progressive Matrices task ($r = -0.44$) and during an arithmetic task ($r = -0.43$) in 72 persons who had suffered a TBI, stroke or hypoxic brain injury.[28] Similarly apathetic brain injured persons showed less of an increase in heart rate and electrodermal response when starting a therapeutic task, suggesting to the authors that apathy is associated with reduced emotional responsivity.[27] These findings might be related to a finding of an association between apathy and "lack of active approach oriented coping"[100] demonstrated in 70 subjects who had suffered a TBI, stroke or hypoxic brain injury. Finally, improvement in verbal fluency,[73,76] Trails B performance,[76] digit span,[73] and on the Buschke-Selective Reminding Test,[73] has been shown to occur in small TBI groups as apathy simultaneously improved with amantadine[76] or bromocriptine.[73]

In disorders of the basal ganglia, apathy has been associated with both executive dysfunction and with slowing. Apathy correlated with the initiation-perseveration subscale of the Mattis Dementia Rating Scale ($r = -0.49$) in subjects with progressive supranuclear palsy,[43] and there was a "significant correlation"[41] between apathy and number of errors on the Stroop test in Parkinson's disease. Apathy was further associated with executive dysfunction in Parkinson's disease as apathetic subjects were more impaired on Trails B (but not Trails A), verbal fluency, and paired associate learning.[6] However, a negative finding, as regards an association with executive dysfunction, also came out of this study, as there was no association with performance on the Wisconsin Card Sorting Test (and neither on digit span). A study of one apathetic patient postanterior communicating artery bleed involving the head of the left caudate[70] demonstrated executive impairment which improved along with improvement in apathy during treatment with bromocriptine. In another case report,[71] a patient who had suffered a subcortical stroke showed a decrease in reaction time as apathy decreased with methylphenidate.

In stroke patients apathy has been associated with decreased amplitude of the novelty P_3 response,[107] duration of viewing of novel stimuli,[107] verbal IQ,[52] and verbal fluency.[52] Apathy also correlated with attenuated

responses to novel stimuli[108] in nine subjects poststroke involving the dorsolateral prefrontal cortex. A review of studies in schizophrenia[102] suggests that negative symptoms are associated with frontal system cognitive impairment. In one study involving schizophrenia apathy was associated with impairment on the Continuous Performance Test[109] and with decrease recognition of facial emotion.[110]

Results from the HIV population have been mixed. Apathy was not associated with performance on a broad range of neuropsychological tests in 133 subjects[57] but was associated with impairment on the Stroop interference task and with slowing of dual task reaction time in another study.[58] In another study, working memory correlated with apathy, as assessed by a number of measures of working memory, with r values ranging from -0.36 to -0.46.[56] In this study apathy did not correlate with reaction time (i.e., in contrast to the finding of slowed *dual task* reaction time reported above).[58]

In summary, while apathy did correlate with general cognitive tests such as IQ, the majority of correlations, particularly in patients with more discrete pathology, were restricted to those measures that have been related to frontal system functions.

Association With Depression

That a relationship between apathy and depression exists is made obvious by observations of similarity in some of the phenomenology and diagnostic criteria in the two syndromes. However, the literature would suggest that not all cases of apathy are caused by depression, and that this is true across a number of disorders. 37% of 319 subjects with AD had apathy as assessed by the Apathy Scale;[14] however, 24% also had depression, yielding a net of 13% who were felt to have "pure apathy." In a similar study by the same group, 42% of 50 subjects with Parkinson's disease were apathetic,[6] but 30% were depressed, and hence 12% had pure apathy. Poststroke rates were found to be 50% for apathy, 20% for comorbid depression, and 30% pure apathy in a study with $N = 40$.[52] Finally 83% of apathetic TBI subjects had comorbid depression, such that only 17% of apathetic subjects had pure apathy.[26]

Apathy also correlates with depression. In 72 subjects with various brain insults, the Apathy Evaluation Scale correlated with a depression measure with $r = 0.42$ ($p = 0.001$).[28] The range of r values for apathy versus a number of measures of depression in an HIV population was from 0.31 to 0.59,[57] while an r of 0.48 ($p < 0.05$) was found for the Apathy Evaluation Scale versus the Geriatric Depression Scale in a geriatric rehabilitation unit.[62] Finally in 353 persons suffering with posttraumatic stress disorder an $r = 0.68$ for the Apathy Evaluation Scale versus the Beck Depression Inventory was found.[111]

There are a number of studies which do not suggest a strong relationship between apathy and depression. In 154 subjects with various insults/illnesses of the brain[12] apathy only weakly correlated with depression ($r = 0.11$). Only in the Parkinson's disease subgroup was a significant correlation found. Nor was there an association between apathy and depression in 26 AD subjects.[18] In another study, the slope of the regressions between apathy and depression were found to be different in AD versus poststroke versus major depression, prompting the authors to conclude that apathy is "discriminable" from depression.[25] In another study by the same group and in the same populations,[112] the Apathy Evaluation Scale was found to correlate only with certain Hamilton Depression Rating Scale items. These items were work/interest, psychomotor retardation, anergia, and lack of insight. The authors conclude that at least part of the association between apathy and depression (e.g., as noted in the studies above) can be explained by the fact that depression measures include items "consistent with apathy." In a treatment study employing methylphenidate in 27 subjects with AD or vascular dementia,[82] there was no association between apathy and depression at baseline, and nor did the level of depression drop as apathy improved with treatment. Similarly depression did not improve, while apathy did, with bromocriptine in 11 subjects post-TBI or subarachnoid hemorrhage.[73]

Association With Age

There are also conflicting findings as regards the role of age in apathy. In 319 subjects with AD,[14] age was the third independent variable to enter the model predicting apathy. R values of 0.31[52] and 0.3[62] were found between apathy and age in subjects poststroke, or in geriatric rehabilitation, respectively. Apathetic subjects were found to be older than nonapathetic subjects poststroke.[53] However, age was found to have no association in four studies involving TBI,[27] Parkinson's disease,[41] dementia with Lewy bodies,[55] and healthy elderly.[113] The latter finding provides hope that apathy is not an inevitable result of ageing.

Apathy does not appear to be associated with illness

severity as assessed by TBI severity,[27] and by stage of illness, levodopa dose, duration of illness, and motor signs in Parkinson's disease.[41] Indeed, apathy appears to be more severe in the early stages of Parkinson's disease.[23] Apathy also did not associate with illness progression in HIV.[57] Apathy does not appear to be associated with fatigue, at least in myotonic dystrophy.[60] It does, however, appear to be associated with neurobehavioral syndromes such as irritability ($r = 0.72$) and disinhibition ($r = 0.67$) in corticobasal degeneration,[43] and with delusions and hallucinations (when controlling for depression) in dementia.[114]

In summary, the findings reviewed above are in agreement with the conclusions suggested by the prevalence and treatment data in suggesting that apathy following insult to the brain is caused, at least in part, by dysfunction of subcortical-frontal circuits which subserve motivation, attention and emotional response to novel stimuli, and executive function. These circuits include the dorsolateral prefrontal cortex, the anterior cingulate, the thalamus, the basal ganglia, and white matter tracts connecting these regions. Other brain regions, such as the orbitofrontal cortex and limbic structures, may also be involved, but the evidence is less compelling for these regions. There are weakly suggestive, but inconsistent, data implicating right versus left hemisphere dominance in producing apathy. Dopamine, acetylcholine, and to a lesser degree norepinephrine and serotonin, appear to be the most important neurotransmitters involved in apathy, and by extension in subserving motivational behavior. Depression appears to be one of many disorders that can cause apathy, yet not all apathy is caused by depression. Depression and apathy appear to share involvement of some subcortical-frontal regions. Apathy is also associated with other neurobehavioral syndromes which are also felt to involve dysfunction of subcortical-frontal circuits, including disinhibition and psychosis. Finally, age may contribute to apathy in some disorders, but the data are inconclusive. Advancing age does not appear to cause apathy in healthy elderly.

SUMMARY AND FUTURE DIRECTIONS

In summary apathy is common, is associated with a host of adverse outcomes, is potentially treatable, and involves dysfunction of critical subcortical-frontal circuits in the brain. These findings should, it is hoped, prompt increased awareness of the need to address apathy across a number of "neurologic" and "psychiatric" disorders. While research into apathy has been plentiful, it is probable that clinicians need to "catch up" to the research, by informing themselves as to (early) detection, diagnosis, and management of apathy. A consensus as to the appropriate clinical definition (i.e., diagnostic criteria) and gold standard for diagnosis is still much needed. Future research directions also include further work on the treatment (see summary of treatment section), and perhaps prevention, of apathy. To this end, further research into the pathophysiology of apathy is indicated. For example, teasing out neurotransmitter receptor subtype involvement may inform pharmacological interventions, while ongoing research into cognitive and behavioral correlates may inform neurorehabilitation strategies.

Ultimately a broader understanding of all of the multiple contributors to apathy will be required before optimal treatment can be hoped for. The biopsychosocial model of behavior would suggest that the research needs to consider other possible contributors to apathy following insult to the brain. Such contributors may include role loss, hopelessness associated with repeated failures, lack of stimulation (e.g., as may occur in long-term care), lack of external reward, pain, sleep disorders, metabolic disorders (e.g., thyroid), premorbid personality and experiences, etc.

Another approach to the future study of apathy would be to consider the model of apathy of Stuss et al.,[3] in which multiple subtypes, depending on which frontal-subcortical system is involved, are proposed. Stuss et al. suggest that involvement of the oculomotor circuit would lead to apathy (as defined by a lack of self-initiated action) for stimuli affected by the involvement of the circuit. For example, patients with contralateral neglect show a type of apathy for the neglected part of their world. It is interesting to consider that apathy may not necessarily involve the entire person's realm of functioning. This is illustrated even more dramatically when considering patients with alien-hand syndrome as seen with involvement of the Supplementary Motor circuit; such patients may demonstrate "apathy," in the sense of reduced initiation of movement of the hand. Involvement of the dorsolateral prefrontal cortex circuit is postulated to result from executive dysfunction, including impairment in cognitive flexibility, planning, novel responsiveness, etc. Involvement of the anterior cingulate circuit, Stuss et al. suggest, may result in apathy due to

a reduction in motivational response directly to external and internal stimuli. Involvement of the orbitofrontal circuit might result in apathy due to lack of limbic affective input, as seen, for example, in frontal leukotomies. Finally, Stuss et al. posit a form of apathy termed "social apathy," which is felt to result from disturbance in the sense of self and social awareness due to lesions in anterior frontal regions. This type of approach to apathy may result in treatments that are better directed to the underlying pathophysiology, and which may hence yield greater efficacy. The causation data reviewed herein provide strong evidence in support of the model of Stuss et al., given that many of the structures involved in these frontal-subcortical systems have been implicated in apathy states. A necessary next step in the testing of the hypothesis of Stuss et al. will be the development of scale(s) to measure the postulated subtypes of apathy.

We have come a very long way in terms of our understanding of apathy, and by extension, our understanding of the neural systems and their interactions, which subserve motivational behavior in humans. We still have much to learn; however, the considerable research efforts to date have laid a very solid foundation from which to better understand, and ultimately address, apathetic behavior in numerous patient populations.

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