

# Negative symptoms and related disorders of diminished goal directed behavior

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Negative symptoms are most widely recognized as being a common feature of schizophrenia and were recognized even in the first clinical descriptions of the disorder by Kraepelin. These negative features can be understood in psychological terms as representing a wide spectrum impairment of goal directed behavior. However, there are many other clinical disorders both within psychiatry and neurology that also involve significant reductions in goal directed behavior. Apathy is recognized as an important factor of many neurodegenerative disorders, including Alzheimer's and Parkinson's diseases. Although they probably represent distinct clinical problems, depression and apathy can often be difficult to delineate. One reason for this is that negative symptoms such as apathy and anhedonia are themselves prominent features of major depression. Indeed, depression can be diagnosed under DSM-IV or ICD-10 criteria in the absence of depressed mood, in which case negative features indicative of reduced goal directed behavior are important symptoms. More extreme examples of reduced goal directed behavior can be seen in neurological disorders such as psychic akinesia, abulia and akinetic mutism. In general, reduced goal directed behavior is observed in disorders in which there is impairment of the prefrontal-subcortical-thalamic circuits. Though the human Kluver-Bucy syndrome is probably best not seen in this way, many of the disorders can be viewed as existing

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**on a continuum of diminished goal directed behavior.**

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In Emil Kraepelin's classic description of what we would now called schizophrenia we find this: "*On the one hand we observe a weakening of those emotional activities which permanently form the mainsprings of volition. In connection with this, mental activity and instinct for occupation become mute. The result of this part of the morbid process is emotional dullness, failure of mental activities, loss of mastery over volition, of endeavour, and of ability for independent action [...] With the annihilation of personal will, the possibility of further development is lost, which is dependent wholly on the activity of volition*".<sup>1</sup>

These days, clinical discussions of impairments of "volition" and "the will" are uncommon. Though as can be observed in the quotation, this would not have been unusual at the time that Kraepelin was making what are essentially the first descriptions of the negative symptoms of schizophrenia.

In modern clinical sciences discussing

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volition and the will would appear to be somewhat taboo, implying a sense of the overly philosophical. Nevertheless, the expression “goal directed behaviour” is sometimes used when discussing certain clinical presentations. Goal directed behavior is taken to mean the multiple inter-related processes and internal states, such as drives and desires, which lead to the initiation and control of action. This action is goal-based because it has a purpose which is to be achieved. The goal could be relatively biological, the achievement being the reduction in basic drives such as for food, water or sexual release. They could be more social or routine based such as starting and participating in conversation, or daily activities such as personal hygiene and organization. These would be said to be goal directed because they involve internal states that provide the causal link between wanting and behaving.<sup>2</sup>

The goal could be more abstract such as the desire to learn information or understand the environment (*i.e.*, curiosity). In such cases the goal is itself a mental state and the actions taken to achieve it may be abstract problem solving and thought. Thus these manifestations are also sometimes called goal directed cognitive behaviour.<sup>3</sup> Despite the apparent neutrality of the expression “goal directed behaviour”, it combines ideas from the neuroscience of reward and motor control with more philosophical concepts of “the will” and “volition”. Nevertheless, central to the concept is the amalgamation of diverse neuroscientific and psychological concepts of motivation, emotion and action into a framework appropriate for interpreting clinical disorders.<sup>2</sup>

Although the concept of goal directed behavior in its current form is relatively new, essentially the same processes and behaviors have long been included in clinical descriptions of disordered behavior. During the early history and development of psychiatry, psychology and neurology the concepts of willed behavior and intention were used openly.<sup>4,5</sup> As can be seen in the quotation above from Kraepelin, clinical descriptions of negative symptoms in “dementia

praecox” date back to 1919<sup>1</sup> and even earlier, in 1880, Charcot (cited by Sacks) had commented on reduced goal directed behavior of patients with Parkinson’s disease, using the word “abulia” to describe them.<sup>6,7</sup> The term abulia will be explored in detail later.

Indeed, until the early 20th century, goal directed behavior, in the form of “intention” or “the will” were important concepts within psychology and clinical brain sciences.<sup>5</sup> Within psychology, behavior was commonly described as being based upon cognition, emotion and conation;<sup>8</sup> the now mainly disused word “conation” meaning “intention”. A variety of psychiatric and neurological syndromes were considered in terms of either diminished or increased willed behavior. Indeed, a clinical distinction which has survived the test of time, covering both traditionally psychiatric and neurological presentations, is Hughlings Jackson’s distinction between positive or “florid” symptoms and negative or “defect” symptoms.<sup>9</sup> Examples of positive or agitated symptoms in neurology include such things as hyperactivity, restlessness, talkativeness, irrational fear, delirium and paranoia.<sup>10</sup> In addition, the term positive symptoms has been extensively used to describe features of schizophrenia such as hallucinations, delusions and thought disorder.<sup>11</sup> These are said to be linked because they display a pathological exaggeration or increase in behaviors and experiences above and beyond those seen in the healthy individual.

Since the late nineteenth century, a wide range of cases and disorders displaying negative or defect symptoms has been described across the clinical brain sciences. At the extreme end, the neurological condition of akinetic mutism presents with a near complete negative syndrome.<sup>12-14</sup> Less severe negative syndromes have been reported in patients with basal ganglia lesions, particularly the globus pallidus.<sup>15-18</sup> These patients have been described as having an “auto-activation” deficit.<sup>16</sup> Patients with neurodegenerative diseases have been described as displaying apathy as a significant part of their overall clinical presentation,

e.g., in Parkinson's disease.<sup>19</sup> Within psychiatry, negative symptoms are well recognized in schizophrenia; however, apathetic states have been noted in people with, for example, depression<sup>20</sup> and substance dependence.<sup>21</sup>

### **Negative and deficit schizophrenia: symptoms, signs and syndromes**

Of course, schizophrenia is the clinical disorder most commonly associated with the concept of negative symptoms. However, it should be noted that schizophrenia is characterised by an extreme variability in clinical symptoms as well as biological features.<sup>22</sup> Patients often present different combinations of symptoms with varying degrees of severity, stability and comorbid features.<sup>1</sup> Attempts to reduce the heterogeneity in symptoms of schizophrenia have produced a number of subtypes, focusing on paranoid symptoms (in the paranoid/non-paranoid distinction), thought disorder (in the thought/non-thought disorder distinction), or negative symptoms (in positive/negative and deficit/non-deficit distinctions).

Technically, the features that are "negative" in schizophrenia are signs, not symptoms, as they can be directly observed.<sup>23</sup> Nevertheless, the term "negative symptoms" rather than "negative signs" has become the normal expression. Furthermore, whether they should be considered as symptoms or as a syndrome is not completely clear. Crow drew upon the negative and positive distinction of Hughlings Jackson to propose a neurobiological distinction between Type I (positive) and Type II (negative) syndromes in schizophrenia.<sup>24</sup> In terms of symptoms, the positive syndrome was characterized by hallucinations, delusions, and thought disorder and the negative syndrome, by affective flattening, poverty of speech, and loss of drive.

The positive syndrome was associated with an acute presentation, good prognosis, absence of intellectual impairment and a good response to neuroleptics (reflecting its basis in functional abnormalities of the

dopamine neurotransmitter system). The negative syndrome on the other hand, was represented by a chronic state of deficit, poor prognosis, intellectual impairment, poor response to neuroleptics and cell loss and anatomical brain changes (reflecting its basis in structural abnormalities). Crow conceptualised the positive and negative syndromes as independent dimensions reflecting different underlying processes, but not necessarily as separate diseases.<sup>11</sup>

Andreasen and Olsen extended upon Crow's dichotomy by focusing on the diagnostic criteria for the symptoms that represent positive and negative schizophrenia.<sup>25</sup> They developed comprehensive rating scales to assess both positive (Schedule for the Assessment of Positive Symptoms; SAPS) and negative symptoms (Schedule for the Assessment of Negative Symptoms; SANS).<sup>26, 27</sup> The SAPS comprises four subscales: hallucinations, delusions, bizarre behaviour, and positive formal thought disorder. The SANS comprises five subscales: affective flattening, alogia, avolition, anhedonia, and attention impairment (Table I). In validating the positive/negative dichotomy, Andreasen and Olsen reported that positive schizophrenia was associated with better premorbid adjustment and lack of cerebral atrophy, whereas negative schizophrenia was related to a lower level of functioning, cognitive impairments and indications of cerebral atrophy.<sup>25</sup>

Extending definitions provided by Andreasen, Kay *et al.* subsequently developed the Positive and Negative Symptoms Scale (PANSS)<sup>28</sup> which indexes positive and negative symptom groupings using an equivalent number (seven). The PANSS also includes 16 general psychopathology items. McGlashan and Fenton conducted a comprehensive review of the studies that have used a range of symptom rating scales including both the SAPS/SANS and PANSS. In summary, they found an association between negative symptoms and poor premorbid functioning and outcome, and a robust relationship between the negative group and abnormal movement, pointing to the validity of the negative subgroup.<sup>29</sup>

TABLE I.—*Comparison of different criteria used to measure negative symptoms in schizophrenia, DSM-IV major depression and apathy.*

Negative symptoms of schizophrenia (26)	DSM-IV major depression (60)	Apathy (3)
Evidenced by:	Depressed mood or markedly	Loss of or diminished motivation,
– Affective flattening or blunting (e.g. unchanging facial expression, decreased spontaneous movements, paucity of expressive gestures, poor eye contact, affective nonresponsivity, lack of vocal inflections)	diminished interest or pleasure + at least 3 of (only 2 if both above are present)	compared with previous function + at least two of:
– Alogia (e.g. poverty of speech and content, thought blocking, increased latency of response)	– Significant change to body weight or appetite	– Loss of self or environmental -initiated behavior.
– Avolition/Apathy (e.g. poor hygiene, impersistence, physical anergia)	– Insomnia or hypersomnia	– Loss of spontaneous or environment driven ideas and curiosity
– Anhedonia/Asociality (e.g. lack of recreation and hobbies, sexual disinterest, inability to feel, intimacy, limited social relationships)	– Psychomotor agitation or retardation	– Loss of spontaneous or emotion or emotional responsiveness.
– Inattention (e.g. inattentive socially or during testing)	– Fatigue or loss of energy	
	– Feelings of worthlessness or guilt	
	– Inability to think or concentrate, indecisiveness	
	– Recurrent thoughts of death	

While there is support for the validity of the negative symptom subtype of schizophrenia, some researchers have argued that there are in fact two forms of negative symptoms. One group has attempted to distinguish “deficit” negative symptoms (negative symptoms that are manifested as enduring traits) from “non-deficit” negative symptoms (reflecting transient negative symptoms, that are secondary to a variety of factors such as neuroleptic side effects, depression, or environmental understimulation).<sup>30</sup> This approach relies on clinical judgement to classify schizophrenic patients into the “deficit” or “non-deficit” groups, and is based on longitudinal observation rather than on cross-sectional assessment. According to the published criteria,<sup>30</sup> primary negative symptoms of schizophrenia that reflect a loss of function (flattened affect, anhedonia, poverty of speech, and avolition) should be present during the preceding 12 months for a deficit classification. Patients with deficit syndrome are reported to have poorer premorbid adjustment and prognostic scores, and greater neurological impairment than non-deficit syndrome patients.<sup>30, 31</sup> In addition, deficit patients have

been found to have more severe abnormalities in neuropsychological and brain morphological examinations.<sup>32</sup>

Cognitively, patients with negative symptoms of schizophrenia have been found to demonstrate impairments in speed of processing and memory, including relatively slow psychomotor speed, reduced ability to generate words, greater perseveration and poor conceptual thinking, object naming, long-term memory, and procedural memory.<sup>33, 34</sup> This range of deficits can be summarized as a slowing of mental activity and global cognitive deficits in patients with negative symptoms.

Evidence from neuroimaging studies suggests some convergence for specific patterns of dysfunction in schizophrenia patients with negative symptoms. Studies investigating baseline neural activity while patients were at rest have shown that negative symptoms were associated with decreased activity in the left dorsolateral prefrontal cortex and left superior parietal association cortex and increased activity in the caudate nuclei.<sup>35</sup> A prominent hypofrontality has also been observed in patients with negative symptoms performing the continuous

performance test.<sup>36</sup> Electrophysiological studies point to slowed earlier information processing and decreased neural synchronization, associated with hypofrontality in schizophrenia patients with negative symptoms.<sup>37, 38</sup>

Cognitive and biological heterogeneity may exist within negative symptoms. For example, Craver and Pogue-Geile found that negative symptoms could not differentiate the siblings of schizophrenia patients from control probands or their siblings. However, they found a trend for the differentiation in anhedonia symptoms, suggesting heterogeneity within negative symptoms.<sup>39</sup> Kirkpatrick *et al.*<sup>40, 41</sup> found that schizophrenic patients who have deficit negative symptoms were associated with familial or genetic aspects of schizophrenia.

### **Apathy: brain systems and neurodegenerative disorders**

It is recognized that schizophrenia is not the only disorder that frequently presents with negative features. Neurological illness is also often associated with patients displaying a significant reduction in goal directed behavior. This is particularly true of neurodegenerative disorders. While in psychiatry such presentations may be described as negative features, in neurology the preferred term has been "apathy". An early clinical definition of apathy was "lack of motivation not attributable to diminished level of consciousness, cognitive impairment, or emotional distress".<sup>42</sup> More recently, a more detailed definition has been made which allows for a clearer diagnosis, this is shown in Table I. This definition suggests that apathy should be diagnosable if there has been a loss of motivation over at least four weeks, providing that at least two other domains of their concept of apathy are also present. They suggest that the three domains of apathy are diminished goal directed behavior; diminished goal directed cognitive activity and diminished spontaneous or responsive emotion.<sup>3</sup>

Such disorders of goal directed behavior

are most commonly associated with frontal lobe dysfunction. The frontal lobe syndrome in neurology has been shown to closely resemble chronic schizophrenia in terms of patterns of negative symptoms and cognitive impairments.<sup>43</sup> This commonality probably reflects the similar underlying neural basis of the disorders, with schizophrenia being particularly associated with dysfunction of the frontal cortex and its interconnections with the basal ganglia.<sup>44</sup>

An influential analysis of connections between the frontal cortex and subcortical structures has emphasized five main circuits.<sup>45</sup> Of these, three are primarily involved with goal directed behavior. The dorsolateral circuit is involved with executive function, the orbitofrontal circuit with response inhibition and the anterior cingulate circuit with motivation.<sup>46</sup> In terms of physiology, all project from the original prefrontal cortical region back to themselves *via* the thalamus and multiple basal ganglia nuclei. These three circuits map very closely onto the neurobehavioural syndromes frequently seen after damage to the said cortical areas of the frontal lobes.<sup>47</sup>

Indeed, the role of subcortical regions in goal directed behavior has been suggested by many authors who have emphasized the importance of the basal ganglia. Indeed, diseases that mainly affect those subcortical parts of the circuits have been shown to be associated with reduced goal directed behavior. Basal ganglia strokes have been associated with "negative symptoms".<sup>48</sup> In another report, a meta-analysis of 240 cases with focal basal ganglia lesions revealed that "abulia" was reported in 13% of all cases and 28% of those with caudate lesions.<sup>49</sup> Abulia is word occasionally used in neurology to indicate a significant loss of motivation; this phenomenon will be examined later.

There is a wide range of neurodegenerative diseases that have been associated with various levels of goal directed behavior impairment. There is a commonality in that all involve the frontal-subcortical-thalamic circuits to some extent. Progressive Supranuclear Palsy also shows a pattern of impair-

ment in brain regions associated with the anterior cingulate circuit, including the thalamic medial dorsal nucleus.<sup>50</sup> This atypical parkinsonian syndrome results from multiple lesions including the caudate, putamen, globus pallidus and brain stem.<sup>51</sup> Apathy is now recognized as an important aspect of the overall clinical picture of Alzheimer's disease, with a prevalence of around 42-55% of cases.<sup>20, 52</sup> In addition, apathy in Alzheimer's disease correlates with executive task performance commonly thought to rely heavily on frontal lobe function.<sup>53</sup>

Parkinson's disease is a classic example of a disease affecting the basal ganglia. Deficits of goal directed behavior in Parkinson's disease were first described over a century ago.<sup>6, 7</sup> Charcot used the term *abulia* to describe the Parkinson's patients he saw and this term has been used occasionally ever since to describe the loss of motivation seen in sufferers.<sup>54</sup> However, the most common description of patients with Parkinson's disease is apathy.<sup>19</sup> This may reflect the nature of the disease producing progressive levels of goal directed behavior impairment, and the overlapping nature of the terms *abulia* and apathy. Apathy, as defined in Box 1, has prevalence of around 27-50% in Parkinson's disease.<sup>20, 55</sup> A sufferer of Parkinson's disease who wrote about his condition has given a first person account of the effect of the disease on goal directed behavior: *"I feel I could move faster if I really wished to do so, but some kind of mental blockage robs me of the will. If I force myself to try to complete some task quickly, my limbs seem to freeze up and my hands shake violently. But I still have the feeling that the difficulty is mental, not physical- all I need is the will"*.<sup>56</sup>

An attempt to use identical diagnostic criteria for apathy over a range of disorders has provided a useful comparison. Mulin *et al.* reported that apathy was found to be diagnosable in 55% of their sample with Alzheimer's disease, in 70% of those with mixed dementia, in 43% of those with mild cognitive impairment, in 27% of those with Parkinson's disease, in 53% of those with schizophrenia and 94% of those with a major depressive episode.<sup>20</sup> It is of particular

interest that apathy was diagnosed in such a high proportion of people with major depression, indicating the significant commonality between these disorders.

### Depression and motivational impairment

Although the most notable symptoms of depression appear to be dysphoria, hopelessness and guilt, it is clear that there is also a negative aspect. Depression has been described as containing an aspect of "sick will".<sup>57</sup> Furthermore, patients diagnosed with major depression have been shown to score highly on scales of negative symptoms designed for use in schizophrenia, and in fact their negative symptoms scores do not correlate with depression scores.<sup>58</sup> In schizophrenia, depression exists independently with negative symptoms, as depression scores were not correlated with scores on negative symptoms.<sup>59</sup> This suggests a negative symptoms dimension in major depression that is independent of the usual symptoms associated with it.<sup>58</sup>

In addition to depressed mood, sufferers of major depression frequently report a lack of interest and anhedonia, often accompanied by general withdrawal from social and occupational roles. Indeed, in practical terms, the most important definitions of major depression are those given by the American Psychiatric Association in DSM-IV<sup>60</sup> and the World Health Organization in ICD-10.<sup>61</sup> In the case of the latter system, depression is described as involving: 1) depressed mood; 2) loss of interest and enjoyment; and 3) increased fatigability. For an ICD-10 diagnosis of depressive episode to be made, at least two of these (1-3), plus other symptoms, *e.g.*, sleep disturbance or loss of appetite must be present. Depressed mood is not an essential part of the diagnosis.

Similarly, in DSM-IV a diagnosis of major depressive episode is based upon the presence of either: 1) depressed mood; or 2) markedly diminished interest or pleasure; plus several other symptoms (Table I). Thus, whether the DSM-IV or ICD-10 crite-

ria are used, depressed mood is given more or less equal weight with symptoms of lack of interest and motivation, and in fact, depression can be diagnosed in the absence of depressed mood, guilt and hopelessness, when only negative symptoms are present. Furthermore, other symptoms of major depression listed in DSM-IV resemble negative symptoms, or at least have some conceptual overlap. These include: psychomotor retardation, lack of energy and hypersomnia.

Depressed mood and lack of interest therefore constitute the two key diagnostic features of major depression. Indeed, it has been suggested that simply asking about these two features is an accurate method to very rapidly screen for major depression.<sup>62</sup> Symptoms of depressed mood and negative features indicative of reduced goal directed behavior appear to have similar incidence levels. In one study of 553 general practice medical outpatients, depressed mood was detected in about 60% and loss of motivation in about 55%.<sup>63</sup> In another study of 829 psychiatric outpatients with depression, the frequencies of specific symptoms were determined. Although depressed mood was the most common, occurring in about 93% of cases, diminished drive was almost as frequent, present in about 88% of all cases. These were the two most frequent symptoms of major depression. Other symptoms linked to reduced goal directed behavior, *i.e.*, loss of energy and loss of interest/pleasure, were also very common, in fact, more common than worthlessness, hopelessness or thoughts of death.<sup>64</sup>

In older adults, presentations of depression without any depressed mood are common.<sup>65</sup> In such cases, motivational impairment and somatic symptoms are often the most important features of the depression. Such depression without sadness is sometimes called "masked depression",<sup>66</sup> though the concept is rarely applied these days.

### **Distinguishing apathy from depression**

Depression and various negative symptoms, such as low motivation and anhe-

donia, are common symptoms of a range of neurodegenerative diseases.<sup>67</sup> Apathy is the most common neuropsychiatric behavioral symptom in Alzheimer's disease, vascular dementia and dementia with Lewy bodies, affecting around 50-60% of patients; the next most common are anxiety and depression, affecting 31-46% of patients.<sup>68</sup> There is considerable overlap, with many patients with these diseases showing both apathy and depression. One study compared a combined group of 154 patients with Alzheimer's disease, fronto-temporal dementia, progressive supranuclear palsy, Huntington's disease or Parkinson's disease. They did not find a significant correlation between scores on assessments for depression and apathy,<sup>69</sup> suggesting apathy in neurodegenerative disorders is a symptom distinct from depression.

Nevertheless, when patients with a diagnosis of major depression, but not neurological illness, are considered the picture is less clear. Using the diagnostic criteria for apathy shown in Table I,<sup>3</sup> 94% of depressed patients were found to be positive for apathy.<sup>20</sup> Clearly depression is closely linked to some negative symptoms, and indeed major depression itself contains negative features that indicate it can be considered a disorder of diminished goal directed behavior. Nevertheless, the presentation of depression is distinguishable from the negative symptoms seen in schizophrenia. It is perhaps best to consider both as disorders that include negative features, though clinically distinct in their presentations.

### **Akinetic mutism**

In 1941 Cairns *et al.* described the case of a 14-year-old girl who showed a profound action impairment.<sup>12</sup> The patient seemed awake and would follow people in the room with her eyes but did not make any other spontaneous movements. She seemed unaffected by painful stimuli and would swallow bitter, as well as sweet solutions that were placed in her mouth.

Speech was absent except for quiet, monosyllabic responses to questioning, limb movements could be made to command. Cairns *et al.* named the syndrome “akinetic mutism”. The crucial difference between this and other similar disorders was the apparent consciousness of the patient and the ability to produce meaningful actions in some circumstances. These factors distinguish akinetic mutism from superficially similar conditions such as the persistent vegetative state, in which there may appear to be wakefulness, but goal directed behavior cannot be elicited.<sup>70</sup>

Investigations of the patient reported by Cairns *et al.* revealed a cyst in the 3rd ventricle that affected surrounding structures, in particular the medial thalamus bilaterally. Surgical intervention produced a remarkable recovery: “Aspiration of the 3rd ventricle cyst was followed by prompt return of vocalisation, speech, interest in her surroundings, emotional feeling and voluntary movement”.<sup>12</sup>

Since this first description by Cairns, several other authors have described similar states. Recently a case of akinetic mutism linked to new onset encephalopathy following a drug overdose has been reported. Extensive white matter and globus pallidus lesions were found on MRI. Similar to the original case described by Cairns, treatment produced a rapid recovery from the akinetic mutism.<sup>71</sup> An earlier report described a patient with lesions to the mesencephalic tegmentum who showed a total lack of spontaneous movement but could grasp with his hands or protrude his tongue on command.<sup>14</sup> A review of eight patients with similar clinical conditions found that seven had lesions in the pons, whilst the other had prominent damage in the globus pallidus.<sup>13</sup>

Akinetic mutism has been interpreted as being indicative of severe loss of motivation.<sup>72</sup> This interpretation rests on the assumption that the patients were fully awake. However, it is unclear to what extent the patients really were conscious. It has been suggested that the loss of goal directed behavior in akinetic mutism is simply

a consequence of the complete absence of consciousness.<sup>73</sup>

Therefore, akinetic mutism needs to be considered in some depth to establish whether this really is a relatively selective goal directed behavior impairment. This is important because such a profound lack of goal directed behavior would not be surprising if the patient were in a stuporous state. A patient described as being “mute, akinetic and indifferent to painful stimuli”,<sup>74</sup> showed a progression of symptoms that went from apathy, through stupor and eventually coma. However, on hospital admission the patient would not respond to questions and eye movements were random. Therefore, consciousness was questionable during the akinetic stage. Furthermore, eye movements that track objects in the environment are not strictly indicative of consciousness, as even patients in chronic vegetative states have been known to do this.<sup>75</sup>

Verbal reports following recovery are also problematic. The patients of Cairns *et al.*<sup>12</sup> and Daly and Love<sup>14</sup> were amnesic for the period of akinetic mutism. Other patients reported in the literature failed to recover<sup>13, 74</sup> and in none of the above cases were neuropsychological tests performed. It is, therefore, unclear whether these cases represent impaired goal directed behavior or impaired consciousness.

Early reports of akinetic mutism tended to be of patients with lesions to the brainstem. This area includes the reticular activating system, a region that has been closely associated with arousal and vigilance.<sup>76</sup> Therefore, impaired arousal, in at least some of these patients, is an alternative explanation.

More recent clinical reports of akinetic mutism have described patients with lesions directly affecting frontal-subcortical-thalamic circuits.<sup>71, 77</sup> In addition, some have included neuropsychological assessments to clarify the mental state of patients. Mega *et al.* reported a patient with bilateral damage to the globus pallidus interna and ventral striatum. This would have been sufficient to disrupt all five of the frontal subcortical circuits described above; however, it would have particularly affected the anterior cin-

gulate circuit due to the ventral striatal lesions. The patient showed a classic akinetic mute state, she could open and close her eyes on request and repeat five word phrases but made no spontaneous actions. Mental state testing revealed disorientation for place and time but intact recognition of family members. The patient could answer some questions correctly but only with “yes or no” responses. She failed to recover and died eight weeks after admission, as such, no meaningful verbal reports of the state are available.<sup>77</sup>

More informative is the case study of a patient who developed a state that probably conformed to the clinical picture of akinetic mutism, though the authors did not describe her in this way.<sup>78</sup> This patient suffered a unilateral lesion that included the left anterior cingulate cortex and supplementary motor area. In the acute stage the patient lay motionless but would track people with her eyes. She could not answer questions verbally but could nod her head to signal comprehension. There was no evidence of bucofacial apraxia and sentence repetition was intact. On the third day, comprehension was formally assessed and seemed to be preserved; she completed a test of performing actions to verbal instructions normally (the Token Test). Recovery was remarkable, after three weeks the patient was able to converse using sentences with no evidence of agrammatism.

This case is of particular interest partly because of the demonstration of intact comprehension, but also because after recovery she was able to describe her experiences during the acute period. She claimed that her mind was “empty”, that “nothing mattered”, she had “nothing to say”, and that her will to move or communicate was “neutralised”.<sup>78</sup> If these introspective verbal reports can be believed, then this indicates that a profound goal directed behavior impairment was present that could not be accounted for by being in a state of reduced alertness or consciousness. In addition, the ability to perform complex actions such as demanded by the Token Test indicates a preserved motor system.

### **Abulia and its relationship to apathy and akinetic mutism**

Akinetic mutism has often been cited as the extreme, but rare, clinical presentation of a goal directed behavior impairment that is more often seen in less severe cases described as apathy or abulia.<sup>79</sup> Abulia is an old medico-psychological term defined as “loss, lack or impairment of the power to will what is in mind”.<sup>80</sup> Severe abulics may spend much of their time awake in bed and rarely speak spontaneously.<sup>81</sup> These days the word “apathy” is more commonly used in neurology than “abulia” to describe loss of goal-directed behavior. It is often stated that apathy is the least severe impairment, akinetic mutism the most severe with abulia falling between these extremes, and that all three represent motivational impairment.<sup>72, 79</sup>

It appears, therefore, at least heuristically, the three syndromes (apathy, abulia, akinetic mutism) can be considered to be related in terms of a gradient of goal directed behavior impairment. Additionally, the term abulia is sometimes used to describe patients that other researchers or clinicians would probably have described as apathetic<sup>54</sup> or akinetic-mute.<sup>10</sup> In light of this confusion, some researchers have used the umbrella term of “apathy and related disorders of diminished motivation”.<sup>79</sup>

Although apathy is currently the most widely used term to describe reduced goal directed behavior in neurology, a variety of other expressions have been used to describe patients that conform to the definition of apathy given above. These include “prefrontal syndrome”,<sup>47</sup> “executive impairment”,<sup>82</sup> “psychic akinesia”,<sup>83</sup> “auto-activation deficit”,<sup>16</sup> “negative symptoms”,<sup>48</sup> “athymhormia”,<sup>84</sup> “disorder of motility”<sup>85</sup> or simply “motivational deficits”.<sup>86</sup> In addition, the primate Kluver-Bucy syndrome allegedly has apathy as one of its main features, and so the human form is considered briefly below as this may constitute a distinct manifestation of reduced goal directed behavior. In addition, psychic akinesia is discussed in order to assess its relationship to the terms apathy and abulia.

## Psychic akinesia

In the 1980s several reports described a remarkable clinical state in patients following globus pallidus damage. The patients were described as having no, or only minor, motor impairments (although in one case that has been reported in catatonic symptoms were also present<sup>87</sup> and normal “intellectual capacities”). Despite their relatively preserved motor function, they showed greatly reduced spontaneous behavior. This manifested in the patients spending much of their time sitting quietly or lying awake in bed. This was named “psychic akinesia”.<sup>15</sup> A key feature was that normal behavior could be produced in these patients in response to external stimulation. This was suggested as showing dissociation between “hetero-activation” and “self-activation”.<sup>88</sup> The patients were thought to be impaired in self-activation but could be roused by elements in the environment, revealing intact hetero-activation. This aspect of the condition was also widely described as “psychic loss of self-activation”.<sup>89</sup>

A further feature of psychic akinesia was only apparent from verbal reports of the patients themselves. This revealed a “mental emptiness” that was disclosed by the patients describing their inner psychological life as a “void”.<sup>18</sup> Furthermore, they claimed never to become bored despite their lack of activity. These two negative features paired with normal motor and intellectual functions were assumed to be characteristic of a newly recognized clinical entity. Indeed, one paper discussed the recently delineated syndrome of “psychic akinesia”, *i.e.*, blunting of affect and loss of internal motivational drives without motor disturbances or intellectual deterioration.<sup>83</sup>

Psychic akinesia is most commonly seen with carbon monoxide poisoning damaging the globus pallidus,<sup>83</sup> though other causes or pallidal damage producing an auto-activation deficit have been reported, such as toxic reaction to wasp sting or methadone overdose.<sup>15, 87</sup> The consistent reporting of pathology in the globus pallidus perhaps suggests that this may be a distinct presen-

tation from abulia or the general motivational deficit seen as part of the frontal lobe syndrome. Nevertheless, there is reason to question the novelty of psychic akinesia. The reversibility of the condition during external stimulation (hetero-activation) is not unique to these patients. It has already been stated that a key feature of akinetic mutism is total lack of spontaneous movement but with some preserved responding. Although patients with psychic akinesia are not suffering akinetic mutism, similar effects have been noted in more able cases. Some frontal lobe damaged patients may be capable of performing complex actions but will not do so without instructions or environmental prompts.<sup>90</sup> Furthermore, the cases described above all showed neuropsychological impairments resembling the frontal lobe syndrome. Neuropsychological testing was limited, but of the eight psychic akinesia cases most often described in the clinical literature, all showed reduced verbal fluency and all but one performed poorly on the Wisconsin Card Sort Test.<sup>15</sup>

The other key feature highlighted as a symptom of psychic akinesia is the mental void reported by most patients. Again, this is not a unique observation. In abulia following frontal lobe damage, similar behavior has been reported. For example: “Abulics generally deny nervousness, worry, tenseness, or depression. They lack awareness of their condition and express little in the way of needs or satisfaction. They do not have temper outbursts or show anger. As far as can be learned by later questioning, patients have no flow of thoughts”.<sup>91</sup>

It appears therefore, that psychic loss of self-activation and psychic akinesia, rather than being new concepts, are consistent with frontal lobe deficits with consequent abulia. This interpretation is consistent with the patients’ lesions predominantly being in the basal ganglia and affecting the frontal subcortical circuits described above. Indeed, in one description of “psychic akinesia” following bilateral thalamic damage, CT scanning revealed hypoperfusion in the medial frontal lobes.<sup>92</sup>

## Klüver-Bucy Syndrome

Although the most common brain areas associated with reduced goal directed behavior are the frontal lobes and basal ganglia, the temporal cortex has also been implicated. Bilateral removal of the temporal lobes including the uncus and hippocampus, produces a striking behavioral change in rhesus monkeys. This syndrome includes visual agnosia (psychic blindness), altered and increased sexual behavior, distractibility and enhanced orality.<sup>93</sup> However, also of note was a placidity and loss of emotional responses such as fear. This has often been interpreted as apathy.<sup>94</sup> Indeed, bilateral temporal lobotomies have been performed in the belief that they would offer relief to agitated schizophrenic patients. In a report of two cases, the first patient initially became apathetic but this was short lived and she was then given a bilateral frontal lobotomy three weeks later. The second patient had already failed to improve following a bilateral frontal lobotomy and was given a bilateral temporal lobotomy. This produced a range of neuropsychological complications but, according to the surgeon "he was calm" and "without any interest in the outside world".<sup>95</sup> Although this seems to show that the human Klüver-Bucy Syndrome includes apathy, the patient already had frontal brain lesions and chronic schizophrenia it is, therefore, difficult to draw conclusions from such a complex (and unethical) pathological case.

Other examples of the human Klüver-Bucy Syndrome have been reported. In one case bilateral temporal lobe removal was performed to control epilepsy.<sup>96</sup> This patient also developed a complex neuropsychological profile that approximated the rhesus Klüver-Bucy Syndrome (*e.g.*, change in sexuality, agnosia, and distractibility). He also initially developed a "reduction of spontaneous activity", and a placid nature (he had previously been prone to violent outbursts). However, the reduction in spontaneous behavior more closely resembled catatonia than apathy, as during these periods he would not respond to any instruc-

tions at all. The placidity could be explained by the curing of his epilepsy, which was the likely cause of his rage attacks. Therefore, this case does not support the notion of apathy as a symptom of the Klüver-Bucy Syndrome in humans.

Patients described as developing the Klüver-Bucy Syndrome as a consequence of disease, such as encephalitis, have also been reported. To some extent these are a better model as they do not have an underlying long-term illness, unlike the surgical patients described above. Again, apathy is not a clear feature of the wider clinical picture. In one, a series of 12 cases were described, all were said to be placid. However, their neuropsychological status was extremely poor. Most developed dementia, aphasia and amnesia as well as the Klüver-Bucy features such as visual agnosia.<sup>97</sup> Therefore, interpretation of the apathetic status would be unreliable. Similarly, of a group of seven children who developed Klüver Bucy syndrome following herpes simplex encephalitis, all showed placidity but this was not associated with reduction in overall goal directed behaviour.<sup>98</sup> Therefore, despite some claims to the contrary, there is actually little support for a reduction in goal directed behavior, at least in the form of apathy, in the human Klüver-Bucy Syndrome.

## Conclusions

The negative symptoms of schizophrenia represent a wide spectrum of reduced goal directed behavior, including reduced capacity for spontaneous thought and emotions and a general lack of motivation. Depression, generally considered an affective disorder actually has a significant negative aspect too, something which has probably been neglected as the depressed or dysphoric mood would generally appear to be most pressing from a clinical care perspective. Nevertheless, from an academic perspective, it is time that the negative features of major depression were more widely recognized. Comparisons of negative features in schizophrenia and depression are likely

to lead to a better understanding of the pathology and clinical care of both disorders.

Furthermore, many of these negative features are seen in other clinical disorders spanning psychiatry and neurology. Whereas the expression "negative symptoms" has been favored in psychiatry to describe what are essentially impairments of goal directed behavior, multiple alternative terms have been used in neurology, the most popular being "apathy". Indeed, apathy is now recognized as a major symptom in a wide range of neurological conditions. Furthermore, more unusual neurological cases occur such as akinetic mutism, which also seem to represent negative syndromes, in that they present with profound reductions in goal directed behavior. Indeed, neurological cases with negative features can be considered as occurring on a gradient of diminished goal directed behavior ranging from the extreme end of akinetic mutism through abulia and psychic akinesia to the relatively less severe cases described as displaying apathy.

If we consider the definitions given in Table I of criteria for negative symptoms, major depression and apathy we can see that there is considerable overlap. Taking for example the affective flattening and anhedonia seen in the negative symptoms profile of schizophrenia, this has similarity with the diminished pleasure feature of major depression and the lack of emotional responses in the diagnostic criteria for apathy. A further comparison could be made of the avolition feature of schizophrenia corresponding in form to the loss of spontaneous or environment driven ideas and curiosity in the criteria for apathy, and to a lesser extent with the loss of interest seen in major depression.

There is a significant commonality across the psychiatric and neurological disorders considered in terms of their underlying pathophysiology. In almost all cases, the disorder is directly linked to frontal lobe or basal ganglia pathology, in other cases there is likely to be hypofrontality caused by more distal pathology. For this reason, the anatomical circuits originating in the

frontal cortex and projecting through the basal ganglia and thalamus<sup>45, 46</sup> represent a useful model for understanding negative symptoms and related impairments of goal directed behavior in the clinical sciences.

## Riassunto

*Sintomi negativi e disturbi correlati della riduzione del comportamento diretto verso un obiettivo*

I sintomi negativi sono largamente riconosciuti come una caratteristica comune della schizofrenia e sono stati individuati anche nelle prime descrizioni cliniche della malattia da parte di Kraepelin. Queste caratteristiche negative possono essere intese in termini psicologici come una compromissione ad ampio spettro del comportamento diretto verso un obiettivo. Tuttavia, esistono molti altri disturbi clinici sia in psichiatria, sia in neurologia che comportano una significativa riduzione del comportamento diretto verso un obiettivo. L'apatia è riconosciuta come un fattore importante di molti disturbi neurodegenerativi, tra cui il morbo di Alzheimer e di Parkinson. Sebbene probabilmente rappresentino problemi clinici distinti, la depressione e l'apatia sono spesso difficili da discriminare, per esempio perché i sintomi negativi come apatia e anedonia sono essi stessi caratteristiche importanti di depressione maggiore. Effettivamente, la depressione può essere diagnosticata secondo i criteri di DSM-IV o ICD-10 in assenza di umore depresso, nel qual caso, le caratteristiche negative indicative di riduzione del comportamento diretto verso un obiettivo sono sintomi importanti. Esempi più estremi di riduzione del comportamento diretto verso un obiettivo possono essere osservati in disturbi neurologici come acinesia psichica, abulia e mutismo acinetico. In generale, la riduzione del comportamento diretto verso un obiettivo si osserva in disturbi in cui sia presente la compromissione dei circuiti prefrontali-sottocorticali-talamici. Sebbene la sindrome di Klüver-Bucy dell'uomo sia probabilmente non osservabile in questo modo, molti dei disturbi possono essere considerati come esistenti in un continuum di riduzione del comportamento diretto verso un obiettivo.

PAROLE CHIAVE: Schizofrenia - Depressione - Apatia - Demenza - Mutismo acinetico.

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