Negative symptoms: the 'pathology' of motivation and goal-directed behaviour

Richard G. Brown and Graham Pluck

In many neurological and psychiatric disorders, including Alzheimer's disease and schizophrenia, symptoms are present that appear to reflect an essential absence of normal movement, cognition and emotional states. These negative symptoms might reflect fundamental impairments in basic brain mechanisms that underlie goal-directed behaviour. Knowledge of the pathology and pathophysiology of these diseases, combined with evidence from basic science, offers opportunities for understanding the neurobiological basis of goal-directed behaviour, particularly the interaction between limbic structures and striato-thalamo-cortical circuits. The study of patients with negative symptoms also provides opportunities for testing cognitive models of goal-directed behaviour, and eventually to map such models onto the neurobiology of both normal and abnormal behaviour.

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IN 1982, ANDREASEN[1] commented on a 'renaissance of interest' in the negative symptoms of schizophrenia following decades of clinical attention dominated by delusions and hallucinations. From a modest six articles concerned with negative symptoms published in 1982, the number had risen to over 200 papers published in 1995, a rate that has subsequently been maintained. This growth of interest has been stimulated by several factors:

- A growing awareness of the clinical significance of negative symptoms for the long-term outcome, combined with the development of new pharmacological agents for their treatment.
- Recognition that the same or similar symptoms are shared by patients with a range of psychiatric and neurological disorders, which helps us to understand the neurobiological substrate of the symptoms.
- Growing interest in the cognitive neuroscience of goal-directed behaviour, which prompts the study of negative symptoms to help model the cognitive and motivational processes underlying intentionality, volition and will.

Phenomenology of negative symptoms and apathy

The term 'negative symptoms' has its origins in the writings of Hughlings-Jackson[2], and his distinction between positive or 'florid' symptoms, and negative or 'defect' symptoms. Negative symptoms resulted from a true loss of function, whereas positive symptoms represented the disorganization or exaggeration of existing functions. It was in relation to schizophrenia that negative symptoms found a modern home, as a reworking of Bleuler's original description of the disease 'Many schizophrenics ...sit about ...with expressionless faces, hunched up, the image of indifference. They permit themselves to be dressed and undressed like automatons, to be led from their customary place of inactivity to the mess hall, and back again without expressing any sign of satisfaction or dissatisfaction'[3]. Such features are reflected in the instruments now used to assess negative symptoms in schizophrenia, such as the Scale for the Assessment of Negative Symptoms (SANS)[4]. SANS has demonstrated its clinical validity and utility on numerous occasions, reinforcing the importance of negative symptoms in the overall characterization of schizophrenia and as an important indicator of clinical outcome. However, several questions remain unanswered. First, are negative symptoms a primary or core feature of the disease, or merely a secondary consequence to medication, depression or a psychosocial response to the positive symptoms? Second, are negative symptoms observed only in schizophrenia and therefore useful diagnostically, or are they more widespread? Information relevant to both of these questions can be found from looking beyond schizophrenia to other disorders.

In recent years, Marin[5] has championed the view that negative symptoms of the type observed in schizophrenia are common to many neurological and psychiatric disorders. He uses the term apathy to describe them at both a symptom and a syndrome level. Phenomenologically, apathy has considerable overlap with negative symptoms, covering aspects of overt behaviour, cognition and emotion (Table 1).

Negative symptoms and apathy in neurological disorders

Recent case reports and series (for example Refs 6,7), plus group studies that used standardized instruments such as the SANS, Apathy Evaluation Scale (AES)[8] and Neuropsychiatric Inventory (NPI)[9] have greatly increased our appreciation of the widespread occurrence of apathy or negative symptoms in neurological disorders (Table 2).

As with negative symptoms in schizophrenia, doubts are often raised about the status of apathy as a distinct neurobehavioural phenomenon separate from other symptoms, particularly depression. Part of the problem lies in areas of symptom overlap between depression and apathy and is reflected in clinical assessment instruments[24]. In almost all reports, both apathy and depression were found in the sampled patient groups. However, within patients, apathy can be present in the absence of depression and vice versa, and across groups

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the severity of depression and apathy are typically only weakly associated. Differences also exist in the relationship of depression and apathy to other clinical features and symptoms[17]. Most important is the robust association between the degree of apathy (but not depression) and the degree of cognitive impairments, particularly executive functions. Although depression can also manifest with many negative symptoms, important phenomenological differences exist[25]. For example, in apathy there is typically: (1) an absence of subjective distress; (2) an absence of negative thoughts about self, present and future, and (3) a general lack of responsiveness to positive and negative events (compared with the biased perception or response to the two types of events in depression).

TABLE 1. The clinical phenomenology of negative symptoms and apathy

Negative symptoms in schizophrenia[a]	Negative symptoms in apathy[b]
Alogia	**Overt Behaviour**
Poverty of speech	Lack of productivity
Poverty of content of speech	Lack of effort
Blocking	Lack of time spent on activities of interest
Increased latency of response	
Avolition-apathy	Lack of initiative and perseverance
Impaired grooming and hygiene	Behavioural compliance or dependency on others to structure activities
Impersistence at work or school	
Physical anergia	Diminished socialization or recreation
Anhedonia-asociality	**Cognition**
Decreased recreational interests and activities	Lack of interests, lack of interest in learning new things, lack of interest in new experiences
Decreased sexual interest and activity	
Decreased ability to feel intimacy and closeness	Lack of concern about one's personal health, or functional problems
Decreased relationships with friends and peers	Diminished importance or value attributed to such goal-related domains as socialization, recreation productivity, initiative, perseverance and curiosity
Affective flattening or blunting	
Unchanging facial expression	**Emotion**
Decreased spontaneous movement	Unchanging affect
Paucity of expressive gestures	Lack of emotional responsivity to positive and negative events
Poor eye contact	
Affective nonresponsivity	Euphoric or flat affect
Inappropriate affect	Absence of excitement or emotional intensity
Lack of vocal inflection	
Attentional impairment	
Work inattentiveness	
Inattentiveness during mental status testing	

[a]All categories and descriptions derived from Andreasen[1].
[b]All categories and descriptions derived from Marin[5].

Neurobiological substrate of apathy and negative symptoms

Table 2 reveals a high prevalence of apathy or negative symptoms in patients with pathology involving the frontal cortex and subcortical structures, particularly those with prototypical fronto-subcortical dementia syndromes[26], such as progressive supranuclear palsy (PSP) and frontal lobe dementia. There is no evidence that damage to any one structure, pathway or region is uniquely responsible for producing apathy or negative symptoms. Instead, a network of cortical and subcortical areas is implicated, within which damage, dysfunction or abnormal connectivity leads to an increased probability of the occurrence of these symptoms.

One starting point for understanding this network is the organization of striato-thalamo-cortical circuits proposed by Alexander and colleagues[27], some of which are illustrated in Fig.1. These circuits provide a means by which frontal cortical activity can be modulated by ascending input from the basal ganglia/thalamus via direct and indirect routes. Striatal dopamine-mediated (DA) input from the pars compacta of the substantia nigra (SNpc) and ventral tegmental area (VTA) play a fundamental role in regulating these circuits, and pathophysiological changes in cortical activity can result from depletion of striatal dopamine. One simple hypothesis is that apathy simply represents the summation of extreme, but essentially independent, cortical hypofunction of the various circuits. However, this hypothesis does not accommodate the interactions between these circuits or the roles of inputs from structures outside the loops.

One crucial component is the limbic-ventral-striatopallidal system, or 'motive circuit', which has been suggested as the key to the translation of motivation into action[28,29]. Many limbic structures, including the amygdala and hippocampus, send outputs to the ventral striatum (particularly the shell region of the nucleus accumbens) and from there into the striato-thalamo-cortical circuit. Direct limbic input into the same circuit is also provided at the level of the thalamus, where it coincides with the indirect amygdalo-striato-pallidal signal (but with opposite net sign), and to the medial orbitofrontal and cingulate cortices themselves[30].

The VTA provides dopamine-mediated input to the ventral striatum (with reciprocal GABA-mediated inhibitory feedback) and other limbic structures, as well as to the cortex itself, via the mesolimbic and mesocortical systems. The cortical DA release modulates descending cortico-striatal fibres, thus potentially influencing the activity of the various striato-thalamo-cortical circuits. Another such modulatory opportunity is offered by the output from the ventral striatum, influenced by both limbic and descending cortical input, which diffusely and non-topographically innervates the SNpc (Ref. 31) and from there affects most of the rest of the frontal cortex.

Even with this simplified description, it is clear that there are many possible pathological and pathophysiological changes, which could disrupt the circuitry and contribute to the negative symptoms. For example, degeneration of the VTA is found in demented individuals with Parkinson's disease[32] who typically show apathy, and also in Alzheimer's disease[33]. Non-dopamine-related pathology, such as the degeneration of the cholinergic pedunculo-pontine tegmental nuclei might contribute to the high levels of apathy in PSP (Ref. 34). These structures form another possible centre for the integration of the motor information provided by the dorsal striatum with the motivational or limbic information, and are implicated in a range of neurological and psychiatric disorders[35]. In schizophrenia and depression, much attention has been focussed on the same network of limbic, striatal and cortical structures[36], with particular attention to the nucleus accumbens and amygdala[37].

The roles of such structures and circuits in the domains of emotion and motivation have been reviewed in detail elsewhere[38,39]. A role for dopamine within this circuitry, particularly at the levels of the dorsal and ventral striata, might be in the signalling of primary rewards and reward-predicting events[40]. Mesolimbic dopamine in particular, might be crucial

TABLE 2. The frequency of negative symptoms and apathy in individuals with neurological disorders

Assessment instrument	Patient group(s) (sample size)	% with apathy or negative symptoms[a]	Notes	Ref.
AS	Cerebrovascular lesion ($n = 96$)	18.8% (9.4/9.4)	Apathy without depression associated with older age and lesions to the posterior limb of the internal capsule.	10
AS	Idiopathic Parkinson's disease ($n = 50$)	42.0% (12.0/30.0)	Apathy associated with older age and executive dysfunction.	11
AS	Questionable or probable Alzheimer's disease ($n = 184$)	54.6% (15.7/38.9)	Apathy associated with greater impairment on tests of verbal memory and executive function.	12
AES	Traumatic brain injury ($n = 28$) Cerebrovascular insult ($n = 30$) Hypoxic brain damage ($n = 14$)	46.4% 56.7% 78.6%	All patients past acute injury (average 12 months). Higher rates of apathy found in right hemisphere damage and subcortical damage.	13
AES	Myotonic dystrophy ($n = 36$) Charcot-Marie-Tooth disease ($n = 13$)	58.3% 0.0%	Apathy unrelated to disease duration or severity, or hypersomnalence.	14
NPI	Idiopathic Parkinson's disease ($n = 139$)	16.5%(4.3/12.2)	Community sample from epidemiological survey. Significantly higher rates of apathy in demented patients. Apathy associated with executive dysfunction.	15
NPI	Probable Alzheimer's disease Mild ($n = 17$) Moderate ($n = 20$) Severe ($n = 13$)	 47.0% 80.0% 92.0%	Apathy increased with severity of cognitive impairment, but unrelated to changes in depression.	16
NPI	Probable Alzheimer's disease (mixed severity) ($n = 30$) Front-temporal dementia ($n = 28$) Parkinson's disease ($n = 40$) Huntington's disease ($n = 34$) Progressive supranuclear palsy ($n = 22$)	 80.0% (43.0/37.0) 90.0% (61.0/11.0) 33.0% (5.0/28.0) 59.0% (21.0/38.0) 91.0% (77.0/14.0)	Depression and apathy severity unrelated overall. Mean apathy rating significantly higher than depression in Alzheimer's disease, fronto-temporal dementia and progressive supranuclear palsy groups.	17
NPI	Corticobasal degeneration ($n = 15$) Progressive supranuclear palsy ($n = 34$)	40.0% 82.0%	Cortico-basal degeneration patients characterized by low apathy and high depression. Depression and apathy unrelated in progressive supranuclear palsy.	18
NPI	Multiple sclerosis (stable) ($n = 44$)	20.0%	Apathy severity unrelated to MRI determined lesion severity or location.	19
NPI	HIV-1 positive AIDS ($n = 26$) HIV-1 positive (non-AIDS) ($n = 22$) Non HIV-1 positive ($n = 21$)	54.2% 13.6% 0.0%	Apathy associated with working memory impairment.	20
SANS-AD	Probable Alzheimer'sdisease ($n = 24$) Elderly controls ($n = 26$)	ND	Neither group depressed. Alzheimer's disease group more negative symptoms overall – severity increased with cognitive impairment. Alzheimer's disease group more symptoms of avolition-apathy and social-emotional withdrawal but not affective blunting.	21
SANS PANSS	Non-aphasic right-handed patients with single strokes in basal ganglia ($n = 9$) or elsewhere ($n = 11$)	ND	Basal ganglia patients showed significantly higher symptom scores of SANS and PANSS (negative) but not PANSS (positive) or depression.	22

[a]Overall % (% without/with co-morbid depression), ND indicates no reports.

Abbreviations: AES, Apathy Evaluation Scale[8]; AS, Apathy Scale[11]; NPI, Neuropsychiatric Inventory[9]; PANSS, Positive and Negative Symptom Scale[23]; SANS, Scale for the Assessment of Negative Symptoms[4]; SANS-AD, Scale for the Assessment of Negative Symptoms in Alzheimer's Disease[21].

for learning associations between contextual stimuli and subsequent reinforcement outcome[41]. Such activity has been suggested to have a key role in learning and in the control of voluntary behaviour[42] and has obvious relevance to the behavioural, cognitive and emotional aspects of negative symptoms. Pharmacological agents that act directly on the dopaminergic system, such as amphetamine, methylphenidate and bromocriptine, have been shown to be clinically useful in some patients[43], although there is little evidence for any significant clinical effect on the apathy in patients with Parkinson's disease. The cholinergic system has also provided a route to the management of negative symptoms. In Alzheimer's disease, the new generation cholinersterase inhibitors have demonstrated a broad efficacy in improving so-called 'non-cognitive' symptoms, including apathy[44]. However, as with the atypical neuroleptics that have a similar impact in schizophrenia, the final neurochemical and neuroanatomical pathways through which they affect behaviour remain unclear.

Goal-directed behaviour and motivation

Although we might appreciate the phenomenology of negative symptoms and have some idea of their possible neurobiological substrate, we lack a frame-

work of the normal cognitive processes that are involved. One such framework is explicit in the Marin formulation of apathy; that it is a reduction in GDB owing to impaired motivation[5].

Within neuroscience, the construct of GDB is increasingly being used to operationalize a broad spectrum of purposeful actions and their determinants, from the simplest single-joint movement, to the most-complex patterns of behaviour. GDB is construed as a set of related processes by which an internal state is translated, through action, into the attainment of a goal[42]. The 'goal' object can be immediate and physical, such as relieving thirst, or long-term and abstract, such as being successful in one's job or the pursuit of happiness. By 'directed' it is meant that the action is mediated by knowledge of the contingency between the action and the outcome[45]. Central to the GDB model is the functional integration of motivational, emotional, cognitive and motor processes, making it a natural framework for bridging the neurobiology and the clinical phenomena of negative symptoms (Box 1 and Fig. I).

Concluding remarks

The GDB model, although complex, serves to highlight the differences between simple movement and purposeful GDB. It places cognitive, motor, emotional and motivational processes within an overall system that subserves GDB and helps to oppose the tendency to view such processes in isolation. It is obviously tempting to map the motivational, emotional, cognitive and motor components of such a model to the neuronal structures and circuits outlined in Fig. 1. For example, it is relatively easy to identify 'executive' and 'motor' modules that might correspond to discrete striatal-thalamo-cortical circuits or the cortical components [e.g. dorsolateral prefrontal cortex (DLPFC) and supplementary motor area (SMA) or premotor cortex (PMC)]. In addition, one might consider the diffuse role of motivational processes at all stages, from the properties of the intentions and the goal representation, through learning and reinforcement, to the drive to initiate and sustain behaviour. Conceptually, this fits well with the multiple direct and indirect influences of the limbic system on striatal, thalamic and cortical structures (Fig.1) and is consistent with Marin's formulation of apathy as primarily a motivational disorder.

However, an exercise in fitting two speculative models is premature and gives a false sense of understanding the system and its dysfunction. Although we should be mindful of the neurobiological constraints when formulating cognitive models[46], further detailed work is required to characterize GDB and its dysfunction. For example, although the GDB model allows for both internally generated and externally triggered routes to action, it is the first of these that is most characteristically impaired in patients with negative symptoms, at least when it comes to the in-itiation of simple and immediate behavioural responses. Impairments in volitional or 'willed' behaviour are typically contrasted with a relative preservation of overt behaviour that is directly cued by an environmental event. However, more-complex behaviours, with abstract or distant goals might not be sustained or completed even in the presence of an initial external cue, which indicates

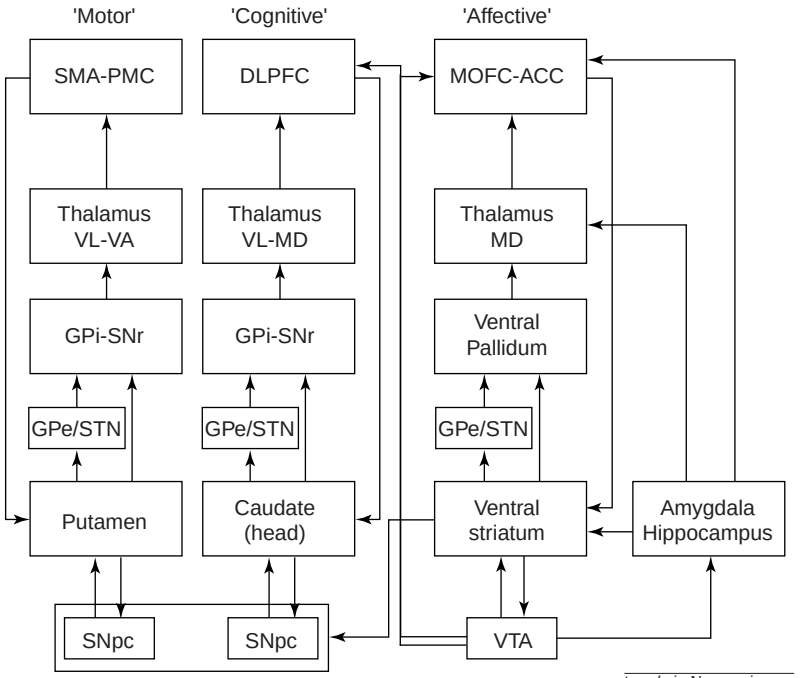

Fig 1. ***Striato-thalamo-cortical circuits and their interactions with limbic structures.*** *The amygdala and other limbic structures involved with motivational and emotional processes, provide input via the ventral striatum, thalamus and cortex. These offer many direct and indirect opportunities for the emotional and motivational processses to influence the activity of other circuits including those concerned with cognition and motor function. Abbreviations: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; GPe, globus pallidus external section; GPi, globus pallidus internal segment; MD, mediodorsal; MOFC, medial orbitofrontal cortex; PMC, premotor cortex; SMA, supplementary motor area; SNpc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VA, ventroanterior; VL, ventrolateral; VM, ventromedial; VTA, ventral tegmental area.*

the overall importance of internal processes in GDB. More information about these processes is required, such as the influence of reward on learning and behaviour in health and disease, and particularly its interactions with cognitive and emotional processes. In addition, constructs such as 'hedonia' and 'drive', although easi-ly invoked, are poorly understood. Finally, little is known about the fundamental representations that underlie GDB, including intentions, and how these might be affected in individuals with neurological and psychiatric disorders. The study of different groups showing reduced GDB provides a valuable opportunity to dissociate the many interacting processes that subserve this meta-function to which so much of the resources of the brain appears to be devoted.

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Box 1. A neuro-cognitive and neuro-philosophical formulation of goal-directed behaviour

There is no one model of goal-directed behaviour (GDB). Rather, different approaches from philosophy to basic science, have sought to address different aspects, from cognitive formulations of will and volition[a] and their functional anatomy[b] to the neurobiology of reward[c] and their roles in the control of purposeful behaviour. Figure I attempts to synthesize the key characteristics and prerequisites of GDB as reflected in such contemporary models.

Purposeful behaviour is driven by an internal process or intention (1). This can be a conscious 'wish', 'desire' or 'urge', perhaps arising from some preceding cognitive event, or a relatively automatic state-change in response to an environmental stimulus[d].

These internal states have motivational properties (2), which might be innate (primary reinforcers) or learned through experience. Motivators, by definition, change the probability of a particular behaviour being pursued, and are typically labelled emotionally (3).

A prerequisite of behaviour, if it is to be termed goal-directed, is that the individual must have an internal representation of the goal (4) together with knowledge (although not necessarily conscious awareness) of a causal relationship (5) between a particular course of action and its outcome[a,e]. That knowledge can exist as a conscious expectation or an associative connection.

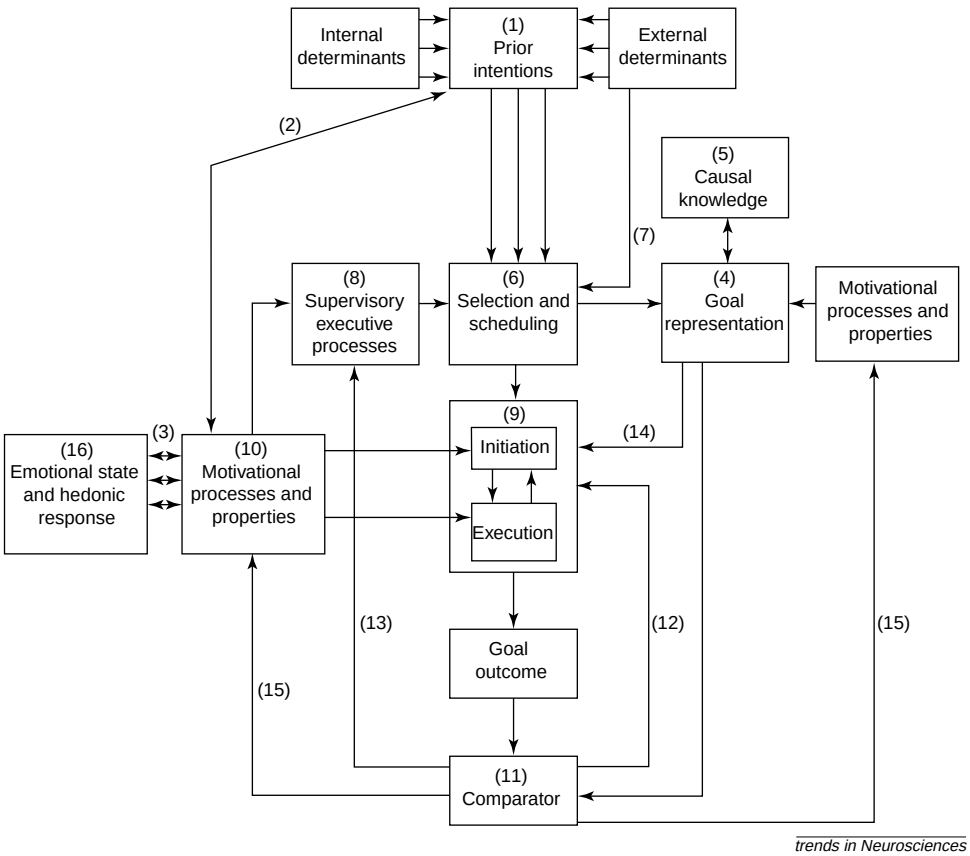

Fig I. ***Representations and processes that are likely to be involved in goal-directed behaviour.*** *Central processing flows from initial intention to goal outcome, through processes of selection, scheduling and performance of the action itself.*

The individual assembles an appropriate serially ordered action programme designed to achieve the goal, perhaps evaluating it against alternatives and selecting the most appropriate (6). These serially ordered subtasks can each be considered 'intentional' even if they are not subject to a conscious 'desire' or 'urge'. Such 'intention to action'[d] can exist in the absence of primary prior intention when the GDB is directly triggered by an external event or occurs in the context of a repetitive or habitual task (7).

In some instances, the individual might need to exert conscious control (8), perhaps inhibiting some habitual response tendencies, which are inappropriate in the present context, or other internal states, which may interfere with the current process[b]. These cognitive operations come under the general label 'executive processes' and involve conscious, controlled and effort-demanding 'supervisory' activity in the control of action[f].

The action or action sequence must be initiated and executed effectively (9) with the intensity and effort determined, in part, by the associated drive properties of the motivational state associated with the goal (10).

Control and maintenance of the activity is achieved through feedback from a comparator (11) evaluating goal outcome against the goal representation. Output from this comparator will serve to maintain or stop the ongoing action (12), and can influence the online modification of the action as the situation demands (13). Where the goal is distant, the action can be sustained by the motivating properties of the goal representation (14), which might be achieved through pavlovian associative processes.

Outcome is associated with a change in the motivational state (15) and associated emotional and hedonic response (16). Goal attainment and reward produces a positive response, maintaining the causal link between the internal state and the action used to achieve the goal and to further increase the likelihood that the behaviour is chosen in the future, through a process of incentive learning. Similarly, failure to achieve the goal leads to a negative response, supporting the adoption of alternative action plans both immediately and in the future.

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Linking DNA damage and neurodegeneration

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Many human pathological conditions with genetic defects in DNA damage responses are also characterized by neurological deficits. These neurological deficits can manifest themselves during many stages of development, suggesting an important role for DNA repair or processing during the development and maintenance of the nervous system. Although the molecular neuropathology associated with such deficits is largely unknown, many of the responsible gene defects have been identified. The current rapid progress in elucidation of molecular details following gene identification should provide further insight into the importance of DNA processing in nervous system function.

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HISTORICALLY, ONE of the most well known connections between abnormalities of the DNA damage response and neurodegeneration has been the human syndrome of ataxia telangiectasia (AT) (Refs 1–3). However, other syndromes associated with a defective DNA damage response also include neurological symptoms as a primary feature of their phenotypes (Table 1). Among these are xeroderma pigmentosum (XP), Nijmegan breakage syndrome (NBS), Trichothiodystrophy (TTD) and Cockayne syndrome (CS). In these cases, the genes responsible for the disease have been identified and are involved in the cellular response to DNA damage. Although many of these genes encode components of DNA-repair complexes, for others, repair deficiencies *per se* might not explain these diseases. Together, these human syndromes provide an important insight into the fundamental processes that affect nervous system function and which probably involve DNA damage.

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Ataxia telangiectasia

Individuals with AT succumb to a devastating progressive degeneration of the nervous system early in life. AT has been characterized as a cerebellar ataxia because of the marked atrophy of the cerebellum associated with Purkinje- and granule-cell loss. The severe

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