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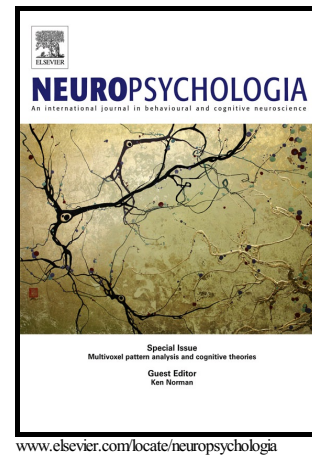
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Apathy following traumatic brain injury: a review

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Abstract

Apathy is a common problem after traumatic brain injury (TBI) and can have a major impact on cognitive function, psychosocial outcome and engagement in rehabilitation. For scientists and clinicians it remains one of the least understood aspects of brain-behaviour relationships encompassing disturbances of cognition, motivation, emotion and action, and is variously an indication of organic brain disease or psychiatric disorder. Apathy can be both sign and symptom and has been proposed as a diagnosis in its own right as well as a secondary feature of other conditions. This review considers previous approaches to apathy in terms of relevant psychological constructs and those neural counterparts most likely to be implicated after TBI. Neurobehavioural disorders of apathy are characterised chiefly by dysfunction of executive control of goal-oriented behaviour or the neural substrates of reward-based and emotional learning. We argue that it is possible to distinguish a primary disorder

of apathy as an organic neurobehavioural state from secondary presentations due to an impoverished environment or psychological disturbance which has implications for treatment.

1.1   Introduction

Apathy is amongst the most common sequelae of traumatic brain injury and can have serious consequences for rehabilitation, such as poor recovery and treatment outcome (Gray et al. 1994; Hama et al. 2007), loss of social autonomy (Prigatano 1992; Mazaux et al.1997), loss of vocational opportunities, with obvious financial implications (Lane-Brown and Tate 2009a), risk of cognitive decline (Dujardin et al. 2007; Robert et al, 2006), caregiver distress (Marsh et al, 1998; Willer et al. 2001), poor quality family life (Marsh et al.1998), and poor social reintegration (Mazaux et al, 1997).

Apathy often occurs alongside other problems such as depression, fatigue and dysthymia which leads to difficulties establishing whether apathy is a primary disorder reflecting neurological damage or part of a broader set of symptoms of an underlying psychological disorder. Definition is also an issue: apathy is also often defined in terms of what it is not, such as a lack of interest, passion, enthusiasm, involvement or initiative. It is different from, but considered similar to, passivity, indifference, ambivalence and dispassion. Without a clear consensus on terminology apathy is used to refer to different facets of experience. This poses a challenge for clinicians for whom accurate description is an essential first step in understanding and

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then treating a condition. In this paper we will review apathy as a neurobehavioural state, focussing primarily as it manifests following traumatic brain injury, and examine the relationship between apathy, motivation and executive function, both conceptually and in terms of neural organisation.

2.1   Apathy after traumatic brain injury

Estimates of apathy following traumatic brain injury (TBI) vary widely from 20 % (Al-Adawi et al. 2004) to 71 % (Kant et al., 1998). The significant variation in prevalence rates probably reflects differences in the definition of apathy and the assessment tools employed (see Table 1). Whereas Van Zomeren and Van den Berg (1985) indicated self-reported apathy complaints in just 16% of chronic severe head injured adults, much higher rates of apathy, in the order of two-thirds, have been reported from relatives (Arnould et al., 2015) and clinicians Andersson et al (1999b).

There is no obvious relationship between the appearance of apathy and severity of the brain injury, whether it is assessed by depth of coma (measured by Glasgow Coma Scale), duration of coma length, or length of post-traumatic amnesia (Van Zomeren and Van den Burg 1985; Andersson et al. 1999a; Glenn et al. 2002; Andersson and Bergedalen 2002). Apathy is generally unrelated to time since injury (Andersson et al. 1999b; Andersson and Bergedalen 2002; Lane-Brown and Tate 2009a) and neither age at injury nor years of education have any significant association with apathy in this population (Van Reekum et al.2005; Andersson and Bergedalen 2002). Although not widely replicated, Kant et al. (1998) reported that younger patients were more likely to be apathetic than older patients who were often

both depressed and apathetic, but that patients with severe injury were more likely to exhibit apathy alone.

Whether the characteristics of apathy following TBI are identical to apathy associated with other conditions such as stroke and degenerative disease is an important but as yet unresolved question. It has implications for understanding the neural basis of apathy in TBI and for potential remedial interventions. It is also important in establishing how far neuropsychological correlates of apathy in one condition can be used to inform cognitive models of apathy in another, and whether there are theoretically dissociable components of apathy such as lack of initiative, lack of interest and emotional blunting which can be used to describe apathy profiles across populations and to drive treatment strategies.

3.1   Assessment of apathy

Lower rates of apathy tend to be identified on the basis of self-report, not only in TBI (Van Zomeren & Van den Berg, 1985) but other neurological conditions such as Huntington's Disease (Chatterjee et al., 2005) and Parkinson's Disease (McKinlay et al., 2008). This may indicate a link between apathy and self-awareness and, by implication, a potential common neural basis, or it may reflect a reluctance to introspect and engage with self-report inventories. Conversely, apathy is often misinterpreted by family members (even professionals) as reflecting laziness or depression while efforts made to energise individuals who are apathetic can elicit aggressive reaction (McAllister, 2008). In this context Guerico et al., (2015) indicated that amongst cognitively intact respondents, self-rating may be a more reliable measure of apathy than third-party reports.

Although several generic neuropsychiatric symptom measures include items pertaining to apathy they are not specific to the condition and often overlap with symptoms of depression and also fatigue. Where different rating scales have been deployed with different conditions, such as the Lille Apathy rating scale in Parkinson's Disease (Sockeel et al., 2006) and the Neuropsychiatric Inventory in dementia (Aharon-Peretz et al., 2000) it is difficult to make comparisons across conditions. The 18-item Apathy Evaluation Scale (Marin et al., 1991a) is perhaps the most widely used instrument, comprising clinicians, informant and self-rating versions, and has proved popular in studies of dementia, an abbreviated version being developed for use with advanced dementia patients in nursing homes (Lueken et al., 2007). A 14-item Apathy Scale, modified from the AES (Starkstein et al., 1992) has not been validated with TBI. In a review of 15 apathy scales or subscales Clarke et al (2011) determined the AES and Neuropsychiatric Inventory to be the most psychometrically robust but evidence of validity for using such scales in TBI is extremely limited. For example, Glenn et al (2002) raised concern that the self-rating and informant rating versions of the AES lacked adequate sensitivity and specificity in TBI. Amongst other measures, apathy is one of three domains (alongside disinhibition and executive dysfunction) of the Frontal Systems Behaviour Scale (FrSBe) and in TBI at least may be more sensitive than the AES to cognitive and behavioural aspects of apathy (Lane-Brown and Tate, 2009a). Recently the much briefer 3-item Apathy Inventory has also been proposed as a sensitive measure of different but highly correlated components of apathy in TBI (Arnould et al., 2015) but this has not been widely replicated.

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4.1   Neuropsychological aspects of Apathy

Although various attempts have been made to consider the nature and severity of apathy in a clinical context the underlying theoretical bases to clinical investigations are rarely scrutinised and is therefore outlined at this point. A cardinal feature of apathy is diminished goal-directed behaviour, which has been defined as a set of related internal processes (motivational, emotional, cognitive and motor) that are translated, through action, into the attainment of a goal (Schultz, 1999; Brown and Pluck, 2000).

Psychology has traditionally distinguished between cognitive, affective and conative aspects of mental life, in which conative processes include those we consider to be especially affected in apathy. This includes motivation, goal-orientation, volition, will, self-direction and self-regulation. Whilst apathy is generally recognised to have cognitive, emotional and behavioural components, different notions of apathy focus on different aspects. Neuropsychology has largely neglected conative processes but they may constitute a crucial link between cognitive ability and prediction of performance in daily life (Reithan and Wolfson, 2000), disruption to which may explain the dissociation between having goals and working to attain them, which characterises some manifestations of apathy.

It can be difficult to distinguish dysexecutive disorder from apathy after TBI because cognitive aspects of apathy usually include executive functions associated with goal-directed behaviour. Alternatively, as apathy is often characterised by waning interest in activity, some authors have suggested that deficits in sustained attention after frontal injury may be the main underlying factor (Daffner et al., 2000). However apathy is not an inevitable outcome of executive dysfunction and attention-

impairment. In terms of conative processes, a distinction can be drawn in the meaning of an incentive to action between an intrinsic 'want' (motivational aspect) and a 'like' (hedonic aspect), either of which may be deficit in apathy. Finally the affective or emotional aspects of apathy are known to overlap with the motivational (such as anhedonia) and cognitive (e.g. negative thoughts) and it is difficult to distinguish truly affective contributions to apathy that are not mediated by cognitive or motivational factors.

One solution was to subordinate the role of the affective dimension in apathy. Hence in Marin's (1991b) original formulation, apathy as a distinct syndrome could be distinguished from apathy as a symptom of other problems (such as emotional distress or an altered level of consciousness). The key feature of the apathy syndrome was a lack of motivation, characterised by diminished goal-directed thoughts and behaviours, a loss of interest combined with indifference to planning or setting goals, plus a lack of effort to achieve simple goals set by others. Thus it focussed on the absence of goals in both cognition and behaviour whilst recognising emotional indifference underpinning a lack of effort to work towards goals.

Marin's apathy syndrome is fundamentally a motivational disorder, though possibly also involving drive, and the AES has also been used as a measure of motivation in rehabilitation (Resnick et al., 1998) despite continuing conceptual ambiguity concerning the relation between components of apathy. The importance of drive was recognised some 50 years ago by Bindra (1968) as being necessary but not sufficient for goal-directed behaviour. Bindra argued that action also requires an incentive-based motivation system alongside a state of motor readiness (arousal). We now recognise that, whereas arousal is a general physiological state necessary for behaviour and drive is primarily the physiological basis for goal-directed behaviour,

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motivation is a complex psychological construct that encompasses diverse cognitive and affective factors. This was a point emphasised by Wood & Eames (1981). They distinguished between disorders of motivation and apathy after TBI by describing drive as a property of the organism, a measure of the initiation of behaviour production, or the size of a response to a stimulus. This is linked to incentive, which relates to the amount of desirability attached to a particular goal, which depends on the balance between the inherent properties of the goal and the particular appetites of the organism. For example, giving a chocolate bar as a reward for effort will hold little attraction if the person dislikes chocolate. Therefore, hedonic responsiveness is a factor in motivation and underpins effort.

The condition can be complicated by dissociative or somatoform features resulting in a lack of hedonic responsiveness. This can mean that the individual's ability to experience pleasure (or pain), often a necessary ingredient to effort and motivation, leads to a lack of motivation. By employing these criteria, motivation can be seen as the amount of effort a person of given drive is willing and able to exert to achieve a given goal. Therefore, in rehabilitation, what may be seen by therapists as a desirable and achievable rehabilitation goal may hold no attraction for the brain injured patient who may be strongly motivated towards other, unrealistic, goals or considers the effort to achieve a designated goal to be excessive in relation to the perceived reward. Patients with an apathetic disposition may determine that there is insufficient incentive in any reward, whether material or social, thereby diminishing the level of motivation and effort otherwise needed to engage meaningfully with the rehabilitation process. The success of rehabilitation after serious TBI depends not only on the individual engaging meaningfully with therapy but also the ability (willingness or initiative) to translate what has been learned into everyday activities.

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Stuss et al. (2000) argued that apathy cannot be clinically defined as a lack of motivation because the assessment of motivation is problematic and usually requires inferences based on observations of affect or behaviour. Thus Stuss et al. suggested that apathy should be defined behaviourally as "an absence of responsiveness to stimuli - internal or external - as demonstrated by a lack of self-initiated action". The construct of initiation which is central to Stuss et al.'s definition was also used by Marin (1991a; 1991b) who noted that a lack of initiative and productivity in apathetic individuals was reflected by a lack of concern about their health and functional status. Certainly the emotional parallels in the apathetic person are reflected in flat affect, emotional indifference and a lack of response to important life events. Yet Marin (1991a) regarded the apathy syndrome as a loss of motivation not attributable to emotional distress, intellectual impairment or disorder of consciousness. This underlies the clinician's problem of distinguishing a primary neurobehavioural disorder of apathy after TBI from its presentation as a symptom of another condition, one that may reflect an extreme end of a normal continuum.

5.1   Apathy as a diagnosis

If apathy as a clinical disorder is to be distinguished from normal experience there must be clear criteria for identifying the condition. Thus Starkstein et al. (2001) proposed a set of diagnostic criteria for apathy, using a DSM format:

(Criterion A): A lack of motivation relative to the patient's previous level of functioning or the standards of his or her age and culture as indicated by subjective account or observation by others.

(Criterion B); The presence for at least 4 weeks during most of the day, of at least one symptom belonging to each of the following three domains: (i) diminished goal-directed behaviour, (ii) diminished goal-directed cognition and (iii) diminished concomitants of goal-directed behaviour.

(Criterion C): The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

(Criterion D); The symptoms are not due to diminished level of consciousness or the direct physiological effects of a substance.

Discussing the nosological status of apathy Starkstein (2008) differentiated apathy from neurological conditions of abulia and akinetic syndromes, and psychological states such as despair and demoralisation, but considered the role of emotion in apathy ambiguous. The affective dimension was given greater prominence in revised consensus criteria proposed by Mullin et al., (2011) amending criterion B to include loss of diminished emotion (spontaneous emotion or emotional responsiveness).

Oddy et al., (2009) considered apathy as primarily a motivational disorder but argued that it is unhelpful to consider apathy as a single syndrome as motivation can break down after TBI due to multiple stages in the process of goal-directed behaviour affecting (i) goal identification (akin to Wood's (2001) *need states*), (ii) goal selection, (iii) plan formation, (iv) initiation, (v) self-monitoring and (vi) review and reinforcement. In this model deficits at any stage may resemble apathy if the primary behavioural manifestation is absence of goal-direction.

Generation of goals is impaired by low arousal or reduced creative or divergent thinking (including bradyphrenia and psychic akinesia) which may present as apathy due to apparent lack of concern as the individual is unable to generate preferred activities or goals. Lack of goal selection is another manifestation of the apathetic individual, and can be due to difficulty suppressing externally triggered (pre-potent) goals to allow willed goals to be pursued (Jahanshahi and Frith, 1998). Alternatively inability to pursue objectives may result from inadequate planning or initiation of activity. One potential difficulty with the emphasis on goal-directed behaviour, without considering the emotional dimension, is that it does not take account that a person may be distressed by their inability to work towards a goal.

This gives rise to the importance of emotion and the significance of reinforcement. According to Hull's (1943) concept of drive strength pursuit of a goal is related to need and the attractiveness of reward. This can be seen as a neurological or social influence on behaviour depending on the nature of the need. The extent to which a goal is perceived as rewarding and valued may also be influenced by a number of psychological factors, not least expectations of efficacy which determine how much effort and persistence people demonstrate to achieve an objective (Bandura, 1977). The perceived effort-to-reward ratio will be of significance as will the goal's congruence with over-arching goals and the individual's values and beliefs. Higher levels of self-efficacy are associated with greater social participation after TBI (Dumont et al., 2004) whilst low-self-esteem is linked to an avoidant coping style (Riley et al., 2010). This suggests that apathy after TBI can therefore be a product of, or become reinforced by, a sense of learned helplessness.

Njomboro and Deb (2014) observed that different aspects of apathy correlated with different patterns of performance on neuropsychological testing. They rated 49

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brain injured adults, including 14 with TBI, using the Apathy Evaluation Scale to identify cognitive, affective and behavioural components of apathy. Affective apathy related to performance on a test of facial emotion recognition whereas cognitive apathy was related to attainment on the Brixton test of concept acquisition. The authors surmised that different facets of apathy had the potential to be fractionated into different neuropsychological subdomains and apathy should not be treated as a unitary syndrome (or symptom).

Extending the theoretical framework even further Arnould et al., (2013) proposed that in addition to cognitive, motivational and affective dimensions apathy should also include reference to personal identity, values and beliefs. The authors argue that people with TBI experience multiple neuropsychological and psychological disturbances as potential mediating variables, and that apathy requires a multifactorial and integrative approach to understanding and management.

6.1   Apathy as a neurobehavioural disorder after traumatic brain injury

Following Marin (1991b) it is important to distinguish between a primary (neurobehavioural) disorder of apathy following TBI and apathy arising secondary to other factors such as an impoverished environment or as a symptom of psychological disturbance. In practice it can be difficult to discriminate between these two causes of apathy but a useful starting point is to understand the organic basis of apathy in terms of importance brain regions commonly affected by TBI and the corresponding neuropsychological deficits. This section provides a framework for understanding how TBI leads to apathy by showing different regions involved. Very little research has been carried out on the anatomical basis for apathy in TBI (see Table 2 for recent

examples) so it is necessary to look beyond TBI studies in order to assess the current state of knowledge and develop a comprehensive scheme for understanding apathy in TBI.

6.1.1 Prefrontal Cortex

TBI typically involves damage to orbitofrontal regions and often implicates ventromedial areas of the prefrontal cortex which Bechara (2004) has argued underlies the decision making deficits observed following orbitofrontal injury. Knutson et al., (2012) studied 176 military veterans with penetrating brain injuries and identified a relationship between apathy and a range of CT-identified left prefrontal cortical pathology incorporating inferior, middle and superior left frontal regions. Different profiles of apathy may arise from lateral prefrontal and medial prefrontal damage. Paradiso et al., (1999) reported that patients with lateral prefrontal damage showed more signs of apathy than those with medial frontal damage, leading the authors to suggest that lateral prefrontal damage may disrupt motivation but leave intact the ability to experience (and report) negative emotions. More recently Guild and Levine (2015) proposed that loss of midline brain volume over time, including medial prefrontal cortex, underpinned apathy in chronic TBI.

In psychological terms decision making can lead to apathy at either the stage of goal formation or the timing of action initiation. Decision making ability draws upon motivation insofar as decision making is linked to incentives to act in a particular way, i.e. towards a specific goal. Damage to ventro-medial prefrontal cortex is linked to a range of deficits in reward sensitivity, emotion based learning and decision making (Young and Koenigs et al., 2007; Glascher et al., 2009).

Ventromedial damage also makes people less inclined to take into account future consequences (Bechara et al., 1994) and thus incentives to action are less effective. Disconnection of behaviour from the corresponding emotional and/or somatic state can lead to failure of emotionally-driven learning necessary to avoid lapsing into apathy. Similarly, failure to associate past behaviour with reward can impede learning. In severe cases medial frontal damage can be associated with abulia and may be mistaken for depression (Forstl and Sahakian, 1991).

Prefrontal cortical damage may also cause apathy as a result of working memory impairment though this involves doroslateral and superior (as opposed to ventral) mesial prefrontal regions (Bechara et al., (1998). Alderman (1996) demonstrated that poor response to conventional operant conditioning methods (reinforcement, extinction and time-out) was related to difficulties on a dual-task exercise, but not to tests of intelligence, memory or executive function. It was proposed that deficits in the central executive component of working memory interfered with allocation of attentional resources and undermined learning.

A number of subcortical structures have also been implicated in action that have implications for understanding apathy in TBI, principally the amygdala, striatum, insula and anterior cingulate.

6.1.2 Amygdala

The role of the amygdala in emotionally driven behaviour has long been recognised (Fonberg, 1972) and is a structure sensitive to damage after TBI (Bigler, 2007). Although associated with fear and rage it may be involved more broadly in

detecting stimulus relevance (Sander et al., 2003) disruption of which may lead to failure to recognise events that require a response. Amygdala damage can lead to failures in perception and recognition of emotional cues (Aggleton, 2000). Gottfried et al., (2003) proposed that the amygdala forms part of a prefrontal subcortical circuit that acts as a 'motivational gate' which receive motivational signals from internal and external sensory processing and mediate stimulus-reward associations. Naqvi et al., (2006) also suggested that the ability of ventromedial prefrontal cortex to register the predictive reward value of a stimulus relies upon the integrity of the amygdala. Consequently amygdala damage may disrupt the emotional impetus for behaviour leading to apathy. However the amygdala may not be acting in isolation. Takayanagi et al., (2013) reported an association between left hippocampal volume loss and apathy, leading the authors to suggest a left amygdala-hippocampal complex mediating apathy after TBI.

6.1.3 Striatum

It is well-established that the basal ganglia contain structures involved in processing reward and mediating behaviour and it is likely that there are several different prefrontal-basal ganglia circuits that can cause apathy. Levy and Czernecki (2006) suggested that a common deficit is the loss of amplification of relevant stimuli to outputs to the prefrontal cortex. In this model apathy may reflect damage to emotional processing required to drive behaviour, executive functions involved in planning and maintaining goals, and an auto-activation deficit needed to initiate thoughts and actions.

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Horvitz (2002) proposed that projections from the orbitofrontal cortex and amygdala to the striatum provide a gating mechanism for incentive motivational (reward) signals that in turn project to motor areas for behavioural response. The dorsal striatum (caudate nucleus and putamen) is a key structure considered to be involved in action selection and initiation due its involvement in action-contingent learning (Balleine et al., 2007). Although unlikely to be damaged in isolation after TBI, damage to corticostriatal circuits, for example as a result of diffuse axonal injury, is likely to be important in undermining the energising function of a basal ganglia-prefrontal motivation network.

6.1.4   Insula

Clark et al., (2008) proposed a role for the insular cortex in risk adjustment. On the Cambridge Gambling Task patients with lesions of the insula maintained a high level of betting as odds of winning reduced. This is consistent with the notion that the insula is involved in representation of somatic states associated with decision making (Bechara and Damasio 2005). Insular cortex activation is also greater during high-risk decisions (Paulus et al., 2003) suggesting this region is involved in mediating behaviour according to anticipated of emotional consequences, especially negative emotional consequences. Conversely lesions to the right insular cortex have been linked to lower behavioural activity levels, and higher reported anergia and tiredness (Manes et al., 1999). This suggests that insula damage may lead to apathy due to loss of emotional valence linked to action. More recently on the basis of fMRI evidence Uddin (2015) has argued that insula dysfunction is common to many neuropsychiatric conditions and forms the basis of a 'salience network' that mediates

processing of relevant stimuli for response. In so doing it receives top-down attention and goal-focussed executive inputs from prefrontal regions and bottom-up sensory, autonomic, visceral and homeostatic input about the internal and external world. On this basis disrupted functional connectivity after TBI and other conditions could lead to reduced insula activation, a hypothesis supported by evidence that changes in resting state fMRI signals from this network are associated with apathy in fronto-temporal dementia.

6.1.5   *Anterior cingulate*

Anterior cingulate lesions are associated with abulia (Siegel et al., 2014) and apathy (Marin and Wilkosz 2005) reflecting the role of the cingulate gyrus in the initiation and maintenance of goal-directed behaviour (Devinsky et al.,1995) and subjective emotional responses (Lane et al., 1997). Different subregions are involved in affective processing (connected to the amygdala) and cognitive processing (connected to parietal and lateral prefrontal areas). It is also involved in sustained attention and error detection and it has been suggested the anterior cingulate undertakes a cost-benefit analysis with respect to action (Botvinick et al., 2004). Damage to the cingulate gyrus is common after TBI (Levine et al., 2008; Niogi et al., 2008) and the complexity of this region and its multiple projections provide numerous means by which a dysfunctioning anterior cingulate may contribute to apathy. In addition to linking medial frontal atrophy to persistent apathy, Guild and Levine (2015) also implicated volume loss in the anterior cingulate in apathy in chronic TBI.

Of potential interest, the fronto-insula cortex and anterior cingulate are the only cortical regions to contain spindle von Economo neurons – found only in

humans, great apes, elephants and cetaceans. It is speculated that they serve to relay outputs of the insula and anterior cingulate to frontal and temporal regions (including perhaps the amygdala) to enable rapid processing of complex stimuli and adaptive behaviour. The role of these unique large cells is unclear but they are considered to be important in social cognition and may comprise part of a network for processing social cues that links to reward. They have not been widely studied in TBI but Fajardo et al., (2008) reported that these cells occur in prefrontal Brodmann area 9 (dorsolateral cortex) which has been implicated in frontotemporal dementia, depression and schizophrenia, all conditions associated with apathy. These tentative associations are intriguing and offer the possibility that they could help explain the onset of apathy.

6.1.6   *Other regions of interest*

Latterly other regions have been linked to apathy such as parieto-subcortical circuits (Moretti and Signori, 2016) but this review has focussed on those structures and pathways for which evidence is strongest and which are most vulnerable in TBI. It is likely that TBI damages multiple cerebral structures and disrupts several different cortico-subcortical circuits linked to motivation, emotional processing and the initiation and regulation of action. For example MR imaging reported by Knutson et al., (2014), whilst linking apathy with prefrontal cortical lesions, also implicated insula and anterior cingulate cortex. Of note, apathy was negatively correlated with measured intelligence post-injury. This is consistent with a finding by Levy et al., (1998) that apathy but not depression correlated with poor cognitive performance in a range of neuropsychiatric conditions. The difficulty of separating primary and

secondary apathy was evident in that apathy correlated positively with measures of fatigue and depression.

Finally, research which may have implications for apathy in TBI concerns reports of apathy as a result of deep brain stimulation (DBS) in Parkinson's Disease. Results have been inconsistent but some studies suggest that electro-stimulation of the subthalamic nucleus (STN) can either exacerbate (Castelli et al., 2007) or produce (Drapier et al., 2006) symptoms of apathy in the absence of depression (see also Drapier et al., 2008). Martinez-Fernandez et al., (2016) reported that 27% of DBS patients were apathetic 1 year after surgery (with no change in pre-surgery measures of depression), but whereas non-apathetic patients showed an improvement in depression post-DBS, apathy was associated with lower health-related quality of life, counteracting the beneficial effects of motor improvement. The authors propose that apathy can arise from withdrawal of dopaminergic medication post-operatively, unmasking degeneration of mesolimbic presynaptic dopamine (DA) terminals or as a delayed dopa-resistant apathy as part of a dysexecutive syndrome.

The role of mesolimbic dopamine for translating motivation into action has long been recognised (Mogenson, Jones & Yim, 1980) and more recently DA depletion has been considered a paradigm for understanding a wide range of deficits in TBI (Bales et al., 2009; Yan et al., 2015). Clinically, dopamine-based medication has been used for some time for treating a wide range of arousal, motivational and executive disorders in TBI despite lack of good evidence for so doing (Barrett, 1991; Muller & Von Cramon, 1994; Whyte et al., 2002). Anecdotal reports of benefit suggest this trend will continue but better quality trials are needed. For example Powell et al., (1996) reported improved spontaneity and motivation in rehabilitation in

11 patients with TBI and subarachnoid haemorrhage following bromocriptine, 8 of whom maintained improvement after treatment was discontinued.

Research on the efficacy of pharmacological interventions for apathy has largely been undertaken with progressive neurological conditions and shown a modest benefit of acetylcholine esterase inhibitors (Drijgers et al; 2009; Berman et al., 2012). Anatomically however there is good reason to believe that dopamine-based drugs may prove fruitful given the importance of mesolimbic dopamine receptors in driving reward. The role of the STN in mediating apathy is a promising avenue to pursue. The STN receives inputs from orbitofrontal cortex, anterior cingulate, insula and supplementary motor area – all regions implicated in apathy after TBI (see Table 2). It is therefore well placed to play a role in a motivation circuit. Zenon et al., (2016) recently demonstrated, in an effort-based decision task, that synchronised activity in populations of STN neurons could be used to predict decisions, arguing that this activity reflected subjective value of reward and subjective cost of effort.

For clinicians, a reductionist approach to treatment is unlikely to offer a panacea given the complex nature of apathy, its multiple aetiologies and diverse manifestations. Alongside any pharmacological treatment one must also consider the role of psychological factors in causing or maintaining apathy. This leads us to consider other conditions and life situations in which apathy occurs as a psychological symptom rather than a primary disorder.

7.1   Apathy as psychological symptom

Whilst apathy is a normal experience it is of clinical relevance when it is pervasive and interferes with adaptive functioning. This review has focussed on the basis for identifying a neurobehavioural disorder of apathy where this can be

distinguished from disorders of executive function after TBI, but we end our discussion with the challenge of discriminating between an organic apathy and a potentially remediable psychological disorder. The intuitive appeal of the syndrome versus symptom distinction belies the difficulty of distinguishing apathy that lies at the core of a clinical presentation from apathy that is symptomatic of another condition. This issue has not been addressed satisfactorily, especially in TBI where both organic and psychological features may dominate the clinical picture.

The same neural substrates are likely to be involved both in reactive psychological states where apathy is a core symptom and in primary neurobehavioural disorders of apathy. For example both apathy and depression have been linked to right hemisphere dysfunction (Starkstein et al., 1989; Andersson et al. 1999b). This may explain the large degree of symptom overlap that makes differential diagnosis clinically challenging. Kant et al., (1998) for example reported a sample of 83 TBI patients seen in a neuropsychiatric clinic of whom 60% showed both apathy and depression, approximately 11% had apathy alone and a similar proportion had depression without apathy. The dissociation of depression from apathy suggests that there is some difference between the two in terms of neuronal pathways and cognitive factors involved.

Apathy is not the most common feature of depression after TBI. Kreutzer et al., (2001) reported a 42% prevalence rate for major depression after TBI in a large outpatient sample of more than 700 adults, the main corollaries of which were fatigue, frustration and poor concentration. It is reasonable to consider that amongst people experiencing such problems some would become apathetic over time and would exhibit less goal-oriented behaviour.

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Marin (1990) argued that the core difference was that the apathy syndrome was not secondary to, and therefore not associated with, emotional distress. Thus it would be illogical to refer to someone *suffering* from apathy, as opposed to despair and demoralisation that can only be understood in terms of the individual's emotional orientation to their future. Levy et al., (1998) argued that apathy should not be assumed to reflect depression and that diagnosis of depression should focus on symptoms of sadness, and feelings of hopelessness, helplessness and worthlessness. Similarly, Marin and Wolkosz (2005) that depression, but not apathy, is characterised by dysphoria. The message here is that either depression or apathy-as-symptom may be identified through the association with negative feeling states, the difference between the two being a matter of affect versus motivation.

Fundamentally apathy is a disorder of motivation i.e. of conative processes, albeit that there are cognitive, affective and behavioural aspects that different perspectives on apathy have emphasised. As a disorder of motivation apathy should be distinguished on the one hand from disorders of movement such as akinesia which may be associated with apathy, and on the other hand from disorders of mood such as depression. Investigating potentially causative medical factors may identify a treatable underlying condition. Similarly, following Arnauld et al (2013) consideration of social, cultural and environmental aspects of a person's life circumstances may shed light on extraneous factors that are potentially ameliorable. This has implications for treatment where apathy in contrast to depression may be receptive to different pharmacological agents (Mann et al., 1995; Roth et al., 2007) and behavioural interventions (Worthington et al., 1997). Although research is in its infancy some studies suggest that apathy may respond well multi-sensory environments (Verkaik et al., 2005) to environmental stimulation such as music therapy (Holmes et al., 2006;

see also Eames (2001 regarding abulia) and motivationally-based behaviour therapy
(Lane-Brown & Tate, 2010).

8.1   Conclusion

This review has covered the conceptualisation, assessment, neuroanatomical
basis and treatment of apathy with reference to TBI. It is a selective review, focussing
on issues of particular relevance to practitioners arising from our experience rather
than an exhaustive review and inevitably reflects the views of the authors. The
evidence base for treatment is sparse (Lane-Brown & Tate, 2009b) but we have
endeavoured to assimilate evidence from a range of sources including RCTs, case
reports and systematic reviews in order to provide a comprehensive account of current
knowledge presented in a manner which is accessible for both researchers and
clinicians.

There are still many aspects of apathy that are poorly understood in terms of
the neurochemical, anatomical, neuropsychological and environmental factors
involved, and progress in understanding this complex condition is likely to advance
on multiple levels. Given the central importance of apathy in recovery from TBI
clinicians should be prepared to embrace developments across disciplines and adopt
an eclectic approach to management, chief amongst which is the need to distinguish
between psychological states that affect motivation and underlying brain injury that
disrupts either the executive aspects of goal-directed behaviour or the neural networks
subserving motivation and reward. We believe that greater understanding of the
varied presentations or subtypes of apathy will assist in mapping clinical profiles to

neurological mechanisms and in turn aid the development of targeted pharmacological and neuropsychological interventions.

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Table 1. Selective review of research reporting prevalence of apathy after TBI

Reference	Sample size	TBI Sample	Mean time since injury	Apathy	Measure used	Comparison group
Van Zomeren & Van den Burg (1985)	*N* = 57	Severe CHI Median PTA 22 days	2 years	16%	Self-report	None reported
Kant et al., (1998)	*N* = 83	Mixed severity	Not specified	71%	Apathy Evaluation Scale	None reported
Andersson et al.,	*N* = 72 (*N* = 28	Presumed severe	Not specified	46%	Apathy Evaluation Scale	CVA/hypoxic group

(1999)	TBI)	(based on CT scan)				
Marsh et al, (1998)	N = 69	Severe TBI (based on GCS)	388 days	54%	Head Injury Behaviour Rating Scale	None reported
Al-Adawi et al., (2004)	N = 80	Mixed severity	8.35 months	20%	Apathy Evaluation Scale	None reported
Ciurli P et al., (2010)	N = 120	Severe TBI	10.6 months	42%	Neuropsychiatric Inventory	Healthy controls
Arnould et al., (2015)	N = 68	Severe TBI (based on PTA)	38.85 months	57%	Apathy Inventory	None reported

TBI = traumatic brain injury; CHI = closed head injury; PTA = Post traumatic amnesia; CVA = cerebrovascular accident.

Table 2 1. Relationship of neuroanatomical regions to Apathy following Traumatic Brain Injury

Reference	Sample size	Conditions	Paradigms	Neuropsychological tests	Neural structures implicated
Andersson et al., (1999b)	72	TBI, CVA, hypoxia	Comparison between groups And between lesion localisation	AES; MADRS	Right hemisphere; Limbic Basal ganglia; Hippocampus
Knutson et al., (2012)	176	TBI vs healthy control	Patient – Control comparison of CT and psychometric tests	NRS, WMS; NPI; MMSE; BDI; SCID	Left frontal lobe, Anterior Cingulate; SMA
Takayangi et al., (2013)	10	TBI vs Schizophrenia Vs healthy controls	TBI – Controls comparison of MRI and psychometrics	SCID; AES; SCAN; SANS; SAPS; RCFT; HVLT-R; NART; BVMT-R;	Hippocampus

					mWCST
Guild & Levine (2015)	60	TBI	Correlation of MRI and Psychometric tests	NRS, HIF, DEX, SIP	Medial prefrontal cortex Cingulate gyrus

SMA = Supplementary Motor Area. AES = Apathy Evaluation Scale; MADRS = Montgomery-Asberg Depression Rating Scale; WMS = Wechsler Memory Scale; NPI = Neuropsychiatric Interview; NRS = Neurobehavioral Rating Scale; MMSE= MiniMental State Exam; BDI = Beck Depression Inventory; SCID = Structured Clinical Interview for DSM-IV-TR Axis I Disorders; SCAN = Schedule for Clinical Assessment in Neuropsychiatry; SANS = Structured Assessment of Negative Symptoms; SAPS = Structured Assessment of Positive Symptoms; RCFT = Rey-Osterrieth Complex Figure test; HVLT-R = Hopkins Verbal learning Test-Revised; NART = National Adult Treading test; BVMT-T = Brief Visuospatial Memory Test - Revised; mWCST = modified Wisconsin Card Sorting Test; HIFI = Head Injury Family Interview Problem Checklist; DEX = Dysexecutive Questionnaire; SIP = Sickness Impact profile.