‘Give-up-itis’ revisited: Neuropathology of *extremis*

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Abstract

The term ‘give-up-itis’ describes people who respond to traumatic stress by developing extreme apathy, give up hope, relinquish the will to live and die, despite no obvious organic cause. This paper discusses the nature of give-up-itis, with progressive demotivation and executive dysfunction that have clinical analogues suggesting frontal-subcortical circuit dysfunction particularly within the dorsolateral prefrontal and anterior cingulate circuits. It is hypothesised that progressive give-up-itis is consequent upon dopamine disequilibrium in these circuits, and a general theory for the cause and progression of give-up-itis is presented in which it is proposed that give-up-itis is the clinical expression of mental defeat; in particular, it is a pathology of a normal, passive coping response.

KEYWORDS

Death and dying; psychological stress; psychopathology; neuropsychology.

Introduction

The term ‘give-up-itis’ (GUI) was originally applied during the Korean war (1950-1953) to prisoners-of-war (PoW) who following severe trauma developed extreme apathy, gave up hope, relinquished the will to live and died, despite no obvious organic cause. One medical officer and PoW in Korea observed in some of his fellow captives symptoms he could assess without being able to describe them: a listlessness, a look, a turning from reality. When their symptoms appeared in various degrees and varying combinations he could estimate very closely how long a particular man he had come to know well would cling to life [1]. Another stated, ‘It was the feeling of many men, including some of the doctors who survived the experience, that some of the deaths were not warranted by a man’s physical condition. Instead, what appeared to happen was that some men became so apathetic that they ceased to care about their bodily needs. They retreated further into themselves, refused to get any exercise, and eventually lay down as if waiting to die. […] They seemed willing to accept the prospect of death rather than to continue fighting a severely frustrating and depriving environment’, and that this ‘fatal withdrawal’ was not simply a result of physical causes [2].

‘Give-up-itis' was carried forward to describe the same behaviour occurring in PoW camps in Vietnam, especially during 1964-1973, where one PoW, ‘…shuffled around the camp disconnected from the world around him […] he was really not with us. Finally, toward the end of September, he gave up, lay down, and died’ [3]. The term was later applied retrospectively to World War II camps in which deaths from a fatal withdrawal were described [4]. GUI was also reported in Nazi concentration camps where many victims died simply due to a loss of desire to live [5]. Elie Cohen [6] reports that, ‘At Ebensee I found a few times one or two men lying dead by my side in the morning. The evening before I had observed nothing in these people to show that their end was near’. Mary Lindell (in Ravensbrük camp) found that one of her friends, ‘…had given up and died, even though she had no organic illness’ [7].

GUI has also been observed by shipwreck survivors were trauma victims in life-rafts are reported to have given up and died from despair [8], e.g., 'There were seven of us on the raft but the third officer died about two hours before we were picked up. He was very despondent and toward the end he lost heart and gave up and died' (Bosun, 40 hours liferaft, North Atlantic); 'I think a number of the men became dispirited and despondent and it seemed to me they lost the will to live' (Third Officer, 21 days lifeboat, 15 fatalities). Similarly, a medical officer who survived an aircraft crash reported, 'On the next roll call he didn't answer and I saw he had died. That scared me. There was nothing physically wrong with him. I wondered if it was going to be like this: one by one people would stop answering roll call. This was about five hours before rescue' (personal debrief). Nor is GUI a recent phenomenon having been described in the early American Jamestown colony at various times between 1607-1625. Contemporary reports describe a, '…most strange Condition' with colonists showing an inexplicable apathy, lethargy and indifference and, '…most give them selves over, and die of Melancholye' [9]. A century later European slave-traders reported that captive slaves would give up hope and die 'by the sulks' [10].

Two factors stand out in cases of GUI: firstly, there appears to be no identifiable organic cause for a death which seems incomprehensible [11]. Death is psychogenic. For example, a medical officer during World War II describes a slightly wounded soldier who was brought to the hospital: 'He died - although his wound was of no importance and there seemed no other medical cause for his death' [12]; '…some of the deaths did not seem warranted by the physical conditions of the men,' [11]; one woman who had survived a Japanese prison camp in WWII noted, 'I feel very strongly that quite a number of people who died shouldn't have done so but they just gave up' [13]; a Soviet prisoner, after serving his sentence of 3,650 days, was told that instead of release his term had been prolonged indefinitely and that same day he died, '…for no visible reason' [14]. Similarly in 17th Century Jamestown, '… people died who were not mortally ill', and that death,

'…hath proceeded from a disease in itselfe not mortall', [9]. In more recent times the death of a hospital patient has been ascribed to psychogenic death following a surgical operation that he perceived to have been unsuccessful. It is reported that the day after the operation the patient showed the symptoms of regression, resignation, passivity and apathy and died within one day. The autopsy, histopathologic and toxicologic examinations showed no indications as to the cause of death [15]. In another case an active and conscientious 87-year old man one day took to his bed saying that he was going to die, which he did five days later. Clinically, his physician could find no specific cause of death (Dr Chris Brooks, personal communication).

A former inmate of Auschwitz concentration camp suggested that GUI seemed to be largely psychological in origin [16], a view which has been shared across the centuries: in 1620 George Thorpe in Jamestown reported, '…that more doe die here of disease of theire minde than of their body' [9]. Secondly, the lucidity and sanity of GUI victims is never in question and no observation of psychosis has ever been reported even up to death. When spoken to such people would respond rationally and appropriately, but would then revert to their previous state [11] suggesting that, despite the extremity of the situation, basic cognitive functions remain intact.

The key psychological factor in GUI appears to be a reactive syndrome following psychological trauma that includes extreme withdrawal from the environment, e.g. 'The first reaction of those arriving at the [concentration] camps was massive psychological shock that could last from a few days to several weeks. A few were not able to cope with this situation, gave up immediately, and died shortly after their arrival' [17]. Similarly, in a shipwreck incident, 'The men who died all became apathetic and their morale became very low' (Second Officer, lifeboat, North Atlantic). An examination of numerous accounts of GUI suggests that it is a gradual regression from normal, adaptive goal-directed behaviour through diminished executive function and demotivation to psychogenic death described variously as a 'slipping away', a 'passive suicide'

with death coming by itself and the, '…gradual going out of a candle flame' [6]. One survivor of a shipwreck observed four others gradually dying, '…I had no thought people could die so easily. Their heads just fell back, the light seemed to go from their eyes, and it was all over' [18].

Hypothesis

It is proposed that 'give-up-itis' can be understood as a quantitative regression from normal, adaptive goal-directed behaviour that passes through a clinical spectrum from withdrawal, apathy, aboulia and psychic akinesia to psychogenic death. It is hypothesised that GUI behaviour occurs through frontal-subcortical circuit dysfunction, particularly within the dorsolateral prefrontal and anterior cingulate circuits, and is consequent upon dopamine disequilibrium within these circuits.

GUI pathogenesis

Give-up-itis follows a progressive psychological decline (see fig. 1) that maps across the following five identifiable stages:

INSERT FIGURE 1 ABOUT HERE

Stage I GUI: Withdrawal and loss of initiative

The first stage of GUI has been most frequently reported following psychological trauma. The primary response is a psychological withdrawal and a docility coupled with a cessation of reflection and initiative. Victims have been described as showing a marked withdrawal of involvement from the current situation, accompanied by a paucity of emotion, listlessness, indifference and complete absorption and preoccupation with themselves [11]. In 16th Century Jamestown colonists' behaviour was described as a 'withdrawal from life' [9]; in the Korean camps it was a 'fatal withdrawal', and even refugees in safe Swiss camps were noted to become, '… a

passive object of care… who vegetate' [19] and Viktor Frankl employs the same term to describe how the majority of the prisoners in Auschwitz would 'simply vegetate' [20].

Stage I GUI is characterised by a state of social withdrawal with diminished motivation, mood and initiative whilst consciousness and cognitive function remain normal. The individual is intrinsically capable of carrying out normal behaviours, but these are slower in initiation and shorter in duration than before. There is a dependency on others to structure activities and when spoken to these people respond rationally and appropriately but quickly return to their previous state [11]. Their speech and behaviour does not suggest psychiatric disorder which is consistent with the finding that withdrawal or demotivation is unrelated to a diminished level of consciousness, cognitive impairment or emotional distress [21].

It has been suggested that withdrawal from a traumatic situation can be a coping mechanism involving the constriction of overt behaviour and emotional responses although without any disintegration of the personality or the development of a psychosis. The victim is aware of his or her surroundings and what is going on but their own responses are sharply inhibited and suppressed [11]. Such inhibition can be seen as a form of protection which was evident in the Korean camps where the most common initial response was a physical and emotional withdrawal from the whole environment, coupled with an attitude of watching and waiting rather than hoping and planning [22]. However, if left unchecked, this detachment can progress to a reactive syndrome that includes apathy and more extreme withdrawal [23].

Stage II GUI: Apathy

Exposure to extreme trauma, including survival of atomic bombing, PoW and concentration camps, has been reported to result in an 'apathetic syndrome' [23]. Frankl [20] noted in concentration camps that within, '… a few days the prisoner passed from the first to the second

phase; the phase of relative apathy, in which he achieved a kind of emotional death'. An 'apathy reaction' was widely observed amongst PoWs [11] even extending to a profound apathy syndrome [24] and was experienced by one prisoner as a 'demoralising melancholia' [25], and by another as a 'colossal inertia' who stated, 'I remember waking each morning and being unable to get up. I was not tired - I was just apathetic [and] every act, every decision, required an effort out of all proportion to the circumstances' [12]. A similar recent account comes from an Englishman held in a Russian prison during 2003-5, 'Within a few days of our arrival, perhaps a week, a heavy melancholy descended on me. It was different and altogether bigger and more alarming than plain sadness or frustration or anger. It felt almost physical […] For hour upon hour I lay on my back staring listlessly at the ceiling, and soon the smallest task began to feel like the mightiest effort' [26]. Cochrane [12] described the psychopathology of camp trauma as consisting of 'the fate of apathy' and a degree of apathy was noted in every person at some time, the depth and duration of the state varying between individuals. In the camps prisoners are described as slipping into 'relative apathy' after the first stage of psychogenic trauma, taking no interest in their surroundings and ceasing to strive after self-preservation [6, 20]; others describe a 'hopeless lassitude', a 'symbolic death' [13]. People in Stage II GUI are described as being dishevelled, dirty and unshaven, '…even though water be plentiful and he has a razor in his pocket' [12]; and Primo Levi [27] recounts that, '…after only one week of prison, the instinct for cleanliness completely disappeared in me'. Bettelheim [5] noted that this phase typically began when people no longer lifted their legs as they walked, but only shuffled them and Schein [2] refers to the 'shuffling walk' prevalent amongst PoWs. In the 16th Century some spoke of people dying of 'laziness', although it was also recognised as being no ordinary laziness [9]. As with social withdrawal in Stage I GUI, apathy has been suggested as a defensive mechanism, indeed Frankl [20] states that apathy in the concentration camps was a necessary mechanism of self-defence and an 'apathy syndrome' was felt to be an adaptive response in the PoW environment [28].

Apathy is a quantitative reduction in voluntary, self-generated, and purposeful goal-directed behaviour [28], that can arise through personal loss or psychological trauma [30]. It is diminished motivation in the presence of normal consciousness and independent of any cognitive impairments, although it appears to be associated with executive dysfunction [31], difficulties in working memory, planning and the maintenance of goals and sub-goals [29]. Clinical parallels to Stage II GUI exist, e.g. Habib [32] reports a 60 year-old patient who, following a transient ischaemic attack, would remain motionless and speechless, 'shut in profound inertia', which corresponds well with Cochrane's 'colossal inertia'. Habib also describes a 58 year-old patient who every morning would stay in bed until he was encouraged to rise and get dressed. Once dressed, he returned to his bed or sat down in an armchair for the entire day.

Stage III GUI: Aboulia

Unless Stage I (withdrawal) or Stage II (apathy) are checked the GUI syndrome can progress to a state comparable to aboulia; that is, a severe lack of motivation coupled with a dampening of emotional response, continuing lack of initiative, an inability to make decisions and a lack of speech output. Certain groups of captives were observed who remained apathetic, who ceased caring, washing and eating withdrawing further into themselves, and simply lay down and curled up [11]. One person is described as, '…huddled motionless next to a fire, wrapped in a blanket. He was staring emptily into space, a look we had seen all too many times' [3]. The importance of motivated effort for survival was noted by a woman held in a concentration camp, 'I began to look around me and saw the beginning of the end for any woman who might have had the opportunity to wash and had not done so, or any woman who felt that the tying of a shoe-lace was wasted energy' [33]. Similarly, in another camp, '…many inmates ceased to wash. This was the first step to the grave. It was an almost iron law: those who failed to wash every day soon died […] it was an infallible symptom' [34].

In Stage III GUI a person has lost intrinsic motivation but may still be motivated into action by external stimuli that can range from persuasive nurturing, through reasoning, antagonism and even physical assault. There is a dependency on others to initiate action but if motivated externally then actions are performed correctly, however, as with Stage II GUI, once these external motivators are removed the person soon relapses into inertia. This again has parallels in aboulia in which clinical impairment occurs in those motor and cognitive processes that are self-initiated, and a signature feature of this condition is that it can be reversed temporarily by external stimulation with patients able to produce relevant answers and normal behaviours [29]. Lack of initiative and self-activated goal-directed, behaviour suggests continuing executive dysfunction, although purely cognitive functions continue to be spared [32].

An interesting characteristic of this stage, noted in both GUI victims and aboulic patients, is that of the 'empty mind' or a consciousness devoid of any content. This lack of spontaneous mental activity and inability to concentrate was referred to in the camps as 'brain fag' [25] or a 'mental incapacitation' [3], whilst one sea survivor described having, '…a mind like mush' [35] and another had, '…no thought [...] - just nothing [...] I actually thought about nothing [...] there was nothing going on in my mind' [36]. Stage III GUI victims present with both motor and cognitive inertia, which again have clinical parallels: Habib [32] describes a 64 year-old aboulic patient who reported a striking absence of thoughts or spontaneous mental activity; and another patient, a 60 year-old university professor who, when asked what he was thinking, replied 'I'm just thinking of nothing, no idea, no question, no thought at all', suggesting a state of mental emptiness. It has been argued that this 'mental emptiness' represents apathy in the sphere of executive functions and a 'cognitive inertia' is frequently observed in patients with lesions of the dorsolateral pre-frontal cortex (PFC) that are associated with difficulties in activating mental strategies to support goal-directed behavior [37]. Patients will express the feeling that their mind is empty although behavioural, cognitive and emotional abilities can become normal under external stimulation. In other words, the person's

mind is not engaged but is on ‘stand-by’ [38]. This ‘mental emptiness’ is accompanied by emotional responses that are blunted, with anhedonia and difficulty in self-initiating actions or thoughts that lead to a loss of goal-directed behaviour.

Stage IV GUI: Psychic akinesia

Stage IV GUI is characterised by a further reduction in motivation and diminution of executive function, although consciousness and general cognitive function remain intact, as does language ability but not initiation. The transition from Stage III to Stage IV GUI is illustrated in the following account from a PoW in Vietnam, ‘… I stopped eating regularly, stopped bathing, and even stopped caring. I refused to climb off the bed but would just sit in an almost catatonic state. I sat like that for hours, days at a time. In my addled mind, this seemed to be a comforting distraction […] I simply didn’t care anymore’ [3]. Others died inwardly, ‘…they behaved as if they were not thinking, not feeling, unable to act or respond’ [5].

This description of Stage IV GUI is paralleled clinically in psychic akinesia, or athymhormic syndrome, in which patients present with a wakeful state of profound apathy, indifference to pain, thirst, or hunger; an absence of motor or psychic initiative, manifested by a lack of spontaneous movement; and, in certain cases, incontinence; absent verbalisation and a general failure to respond to questions or commands, although, if they do respond, they often express the feeling that their mind is empty [39].

A characteristic often reported during Stage IV GUI is that victims reached a state where they no longer flinched when hit [40]; they did not even trouble to avoid the blows [27], and became insensitive to daily and hourly beatings [20]. Primo Levi [27] describes this state as a ‘zombie-like apathy’ and to him it was a signal of impending death. The blunting of emotional response to the extent that even pain ceases to stimulate is described in the behaviour of a PoW held

in Vietnam who, '…would sit by the fire pit, sometimes so close that he would singe his hair or burn his skin. He didn't even care. [Other PoWs] would implore him to try [to make an effort], but he couldn't try because it was too hard to make himself live anymore' [3].

This lack of response to pain is mirrored clinically in the case of a 19-year old woman, subsequently diagnosed with psychic akinesia, who when visiting a beach with her parents was left in the shade while they went for a walk. On returning they found that their daughter had not moved her position despite the change in the sun's direction and she was admitted to hospital with second-degree burns [32].

If Stage IV GUI is not arrested early then the GUI victim is often reported to regress to an infantile state with thumb sucking and incontinence. One PoW is said to have continually dirtied his clothing and bed, and others had to clean him and clean up after him [40]. Frankl [20] reports prisoners in the camps who would not move and just lay on the straw wet with their own urine and faeces. Similarly, aboulic patients are often reported to be incontinent [41].

Stage V GUI: Psychogenic death

Stage V GUI is the most speculative phase of this syndrome and can be considered a pre-stage to psychogenic death marking the disintegration of an autonomous person. The progression to this final stage is illustrated by Frankl [20] who observed, 'Usually it began with the prisoner refusing one morning to get dressed and wash or to go out on the parade ground. No entreaties, no blows, no threats had any effect. He just lay there, hardly moving. […] He simply gave up. There he remained, lying in his own excreta, and nothing bothered him any more […] Nothing - neither warnings nor threats - could induce them to [live]. And then something typical occurred: they took out a cigarette from deep down in their pocket where they had hidden it and started smoking. At that moment we knew that for the next forty-eight hours or so we would watch them dying'. A

person smoking his own cigarette was significant as prisoners would receive cigarettes for doing dangerous jobs and cigarettes acted as currency in the concentration camps where one cigarette could buy one soup. The only exceptions to this rule were those who had lost the will to live and wanted to 'enjoy' their last days. 'Thus, when we saw a comrade smoking his own cigarettes, we knew he had given up faith in his strength to carry on, and, once lost, the will to live seldom returned' [20].

This pre-stage commonly takes 3-4 days to complete. In the 17th Century it was observed that, 'Men died within three or fours days after lying down with a blanket over their heads', and further that other people could no longer motivate such victims or to, '…terrifie from a shameful death' [9]. One PoW was described as having 'slipped away' despite pleading from an Army doctor to keep on living. His last words were, 'Just tell them where I've been' [40].

The progression from psychic akinesia to psychogenic death follows an intuitively natural path but marked shortly before death by an apparent brief recovery of motivation, executive function and a degree of hedonia as shown, for instance, by victims enjoying their last cigarette. It appears that during this pre-stage the 'empty mind' or cognitive inertia associated with Stage IV has briefly subsided and been replaced with auto-activated thought that can support goal-directed behaviour; however, the paradox is that whilst some goal-directed behaviour has returned the goal itself appears to have become the relinquishing of life.

Frontal-subcortical circuits: role in GUI

Give-up-itis maps across a progressive sequence of behaviours, firstly there is psychogenic trauma which is followed by a progressive demotivation that passes through a spectrum from withdrawal, through apathy, to conditions comparable to aboulia and psychic akinesia before reaching a pre-stage for psychogenic death. The signs and symptoms of progressive demotivation

observed during GUI have clinical parallels that suggest frontal-subcortical dysfunction consequent upon impairment of the prefrontal cortex-basal ganglia system, a key function of which is the voluntary auto-activation and maintenance of goal-directed behaviour [29, 37]. Frontal-subcortical circuits enable a person to interact adaptively with his or her environment and various neuropsychiatric disorders may result from direct or indirect disruption of the integrity or functioning of these circuits [39]. It is proposed that give-up-itis can be interpreted through this frontal-subcortical circuitry particularly through those neural circuits that mediate comparable pathological conditions.

There are five parallel, contiguous but anatomically independent, neural circuits that link specific areas of the frontal cortex to the basal ganglia with a final circuit returning to the frontal cortex via the thalamus [39, 41]. These comprise a motor circuit, oculomotor circuit, dorsolateral prefrontal circuit, orbitofrontal circuit and anterior cingulate circuit. Each frontal-subcortical circuit is an effector mechanism that allows the organism to act on the environment and each one supports circuit-specific behaviour [42]; the motor and oculomotor circuits support motor function; the dorsolateral prefrontal circuit supports executive function; the anterior cingulate circuit supports motivation and the orbitofrontal circuit mediates social behaviour. Neuropsychiatric disorders reflect circuit dysfunction and consequently, impairment in individual circuits produce corresponding behavioural syndromes [43]: executive function deficits occur with impairment of the dorsolateral prefrontal circuit; impairment in the anterior cingulate circuit produces symptoms of apathy and demotivation that in extreme cases are akin to akinetic mutism; impairment in the orbitofrontal circuit produces disinhibition, irritability, tactlessness, obsessive-compulsive disorder and personality change [42].

With respect to GUI the orbitofrontal circuit can be excluded as the victim does not show disinhibition, obsessive-compulsive disorder or personality change; indeed, apart from obvious

demotivation, it is observed that the victim is recognised as the same person he or she was before the onset of GUI. Mild executive dysfunction can be observed as decreased initiative, planning ability and goal-directed behaviour needed to cope within a survival situation, which suggests that the dorsolateral prefrontal circuit may be implicated. Furthermore, internally generated actions, as opposed to externally triggered or stereotyped actions, are also associated with greater activation of the dorsolateral pre-frontal cortex and anterior cingulate circuit [44] and patients with dorsolateral prefrontal lesions can show both apathy and an impaired initiative whilst in disorders of the basal ganglia apathy has been associated with executive dysfunction [45]. The most likely candidate, disruption of which results in behaviour comparable to GUI, is the anterior cingulate circuit (ACC) which comprises the anterior cingulate cortex, nucleus accumbens, ventral pallidum and ventral tegmental area. The anterior cingulate is essential for the motivation and initiation of goal-directed behaviour [46] and facilitates the intentional selection of environmental stimuli based on their internal relevance [41]. Disruption of the ACC produces apathy, aboulia, psychic akinesia or akinetic mutism depending on the severity of the dysfunction [30].

The correspondence between the symptoms of anterior cingulate syndrome and GUI is striking with both patients and GUI Stage IV victims being described as profoundly apathetic with little or no movement, having their eyes open but showing complete indifference to their surroundings and environment; not speaking spontaneously and often responding to questions in monosyllables; eating and drinking only when fed; are incontinent and display no emotions even in pain and are unresponsive to blows and violence [42]. Clinically this form of psychic akinesia is commonly associated with surgical or vascular bilateral lesions of the anterior cingulate and with lesions of the nucleus accumbens (NAc) [32, 47].

It has been suggested that failure to initiate goal-directed behaviour (also known as auto-activation deficit [37]) may be due to a failure in the basal ganglia to activate frontal lobe structures

when behaviour depends upon internalised guidance. With respect to GUI this can be seen as an inability to establish any goal (even the goal of survival) or to make a plan to support that goal, activities that are associated with the frontal lobes. Bettelheim [48] observed that prisoners lived only in the immediate present; they became unable to plan for the future. Furthermore, patients with a damaged ACC have a decreased ability to create new thought processes [43] presenting with cognitive inertia or an 'empty mind' syndrome, suggesting Stage III GUI, and there is a significant reduction in self-generated actions whilst externally-driven actions remain intact [32] which is consistent with behaviours observed in GUI stages I, II and III. However, there is no suggestion that victims of GUI have suffered actual anatomical damage, consequently the pathogenesis of GUI may lie more in the disruption of the regional chemistry of the anterior cingulate circuit.

Dopamine as GUI modulator

The evidence suggests that the most likely neurotransmitter candidate underpinning GUI is dopamine (DA) given its principal role in motivation and modulating the activity of the anterior cingulate frontal-subcortical circuit during willed actions [30, 49]. The dopaminergic system serves to determine reactions to changes, expected or unexpected, in environmental conditions, and is essential for coping with the external world [49]. People with reduced dopamine levels tend towards apathy, lack a zest for life and often have an impairment in routine actions such as walking which is normally slowed and observed as a shuffling gait [50]. This slow shuffling movement has been observed in PoWs and camp prisoners during stage II GUI and is a mark of defeat. Such motor movement is also observed in conditions such as Parkinson's disease (PD) with patients showing a shuffling gait, stooped posture and bradykinesia. However, whereas PD is considered to be a multisystem neurodegenerative disorder with dopamine depletion occurring in the substantia nigra (SN), GUI appears to be more a single circuit dysfunction consequent upon DA disequilibrium in the nucleus accumbens. Whilst there is an indirect link between the NAc and the

SN this is to the dorsal region rather than the ventrolateral region that is implicated in PD. The evidence suggests that PD and GUI have parallel architectures.

In certain clinical conditions differences in the severity of apathy is considered to be at least partly a dopamine-dependent syndrome [51]; aboulia is suggested to be a dopamine-related dysfunction [46], and DA agents are used successfully to counter apathy and treat psychic akinesia [47]. Functional brain imaging studies further suggest that the physiopathology of demotivation can, at least partially, be explained by a dysfunction of the dopaminergic system [52]. Given the concordance between apathetic, aboulic and psychic akinetic patients and stages II-IV GUI it is possible that GUI is also a DA-related dysfunction with the severity of GUI being associated with the level of depletion of DA in the ACC. Clinical studies show that as DA activity decreases behaviours disappear in the following sequence: spontaneous behaviour, internally guided behaviour, conditioned behaviour and externally guided behaviour [53] which is consistent with the observed progression of GUI syndrome. DA depletion is also associated with anhedonia that also presents in GUI and general anhedonia is associated with stress that is uncontrollable and unpredictable [54].

The normal functioning of the dopaminergic system can be disrupted by both acute and chronic trauma [49] with both an increase or decrease in PFC DA levels differentially affecting brain function [55]. DA levels in the ACC, especially the DA neurons projecting from the ventral tegmental area to the NAc, can be disrupted by aversive stimuli [56] which has an important bearing on GUI as the NAc is responsible for behavioural activation, motivational processes, regulating goal-directed behaviour and is functionally associated, although possibly indirectly, with hedonia [57].

Dopamine, coping and defeat

GUI commonly occurs in a traumatic situation from which there is, or is perceived to be, no escape and over which a person has little or no influence. Essentially, the GUI victim sees him or herself as being defeated. Cruickshank [58] thought that many of the behavioural symptoms exhibited by his patients in the Japanese PoW camp at Changi were as much, '…the result of fighting a losing battle' as of the disease. This cognitive appraisal of defeat in GUI victims is important as stress has differential effects on DA levels in the PFC and the NAc which depend on whether the stressful condition is perceived to be escapable or inescapable [58].

It has been suggested that the initial increase in DA release in both the PFC and the NAc represents an arousal response that modulates active coping behaviour to a dangerous situation (escape or control), with DA returning to basal levels in both regions after removal of the stressor [59]. However, if the stress becomes chronic, or is perceived to be uncontrollable or inescapable, then increased dopamine release activated in the medial PFC inhibits DA release in the NAc to below basal levels with a new increase of DA outflow occurring only when the stressor is removed [56, 60].

The increase or decrease in DA transmission reflects different coping styles with high levels of NAc DA associated with an active coping response and inhibition of DA in the NAc being associated with a passive coping response. The active problem-focused approach, which targets the source of stress, is used when the stressor can be controlled or avoided, and the passive emotion-focused approach, that targets the emotional arousal that sustains stress responses, is employed when the stressor is uncontrollable or inescapable [61]. If active coping is not possible then sustained activation of cortical DA production leads to a profound inhibition of NAc DA release resulting in behavioural impairments and abnormalities in mechanisms of motivation, including withdrawal and apathy [60, 62] that are comparable to those observed in GUI victims. The appraisal of the trauma as uncontrollable inhibits DA transmission in the NAc shifting the organism

into passive coping to save energy and reduce risk [56]. Furthermore, this resultant withdrawal and inactivity may serve a 'replenishing' function [63] and supports the idea of withdrawal and apathy, observed in Stages I and II GUI, being an initial adaptive and protective mechanism. Similarly, in both human and animal studies, passive coping is associated with blunting stress-induced emotional arousal [64] which is consistent with field observations that passive behaviours were seen as a form of protection and as a necessary mechanism of self-defence [20, 22].

Individual differences in coping

Individual character or personality may also play a role in GUI; however, it is not clear from observation alone whether a particular premorbid personality is implicated in susceptibility to GUI. Different types of character seem equally vulnerable and some individuals considered stalwarts in normal life would surprise their companions by perishing quickly. One US PoW in Vietnam, described as a strong and sure 'marine's marine', could not cope, curled up in a foetal position and died with the words, 'Wake me when it's over' [3]. There is evidence that individuals show different capacities for coping, or failing to cope, with trauma. Furthermore, in both humans and animals there are individuals who are preferentially active or passive copers [65], and these individual differences in the propensity to adopt active or passive coping strategies appear to be associated with opposite responses in the mesoaccumbens DA system [56] with passive individuals showing a rapid onset of stress-induced inhibition of mesoaccumbens DA release [55].

There is also evidence that coping styles depend on genetic predisposition and that resilience to passivity develops through interactions between a specific genetic makeup and a history of stress [65]. It has been suggested that trauma resilience can emerge from neuroadaptive changes of the mesoaccumbens DA transmission under stress from specific gene-environment interactions [64].

GUI recovery

A common observation was that people died between three days to three weeks from the onset of a 'fatal withdrawal' or GUI if the person was not forced to respond to his environment [1]. It is possible to recover from even extreme stages of GUI as it is to recover from comparable clinical conditions of apathy, aboulia and psychic akinesia, although in the latter cases usually through administering DA agonists such as bromocriptine, ropinirole, etc. Clearly, such drug interventions are not available within a natural traumatic situation but other field-expedient methods for increasing motivation and recovering adaptive, goal-directed behaviour have been reported. Stage I GUI reversal can be achieved through self-motivation that is supported through previous experience or training; Stage II by more effortful self-motivation and external motivators, e.g. friends, family, duty, responsibility etc.; Stage III through strong external motivators, and early Stage IV through very strong external motivators although these may cease to be effective in the latter phase of Stage IV and early Stage V GUI.

It is noted that, whilst various victims took no concerted action towards their own survival, they could be pushed to action by a leader [11]. Many survivors report lethargy being overcome by forced activity as a result of which the sufferer recovered and Nardini [4] observed that the victim would recover within about 10 days if he were compelled to move around every day. The importance of intrinsic motivation for survival was noted by Frankl [20], who was told by a fellow Auschwitz prisoner that to reduce the chance of being selected for the gas chamber he should shave, stand and walk smartly. To do such clearly requires an appraisal that the person has, at least, some control over his situation, has not accepted mental defeat, and to achieve this both the PFC and the ACC must be functioning.

There are occasions when a victim is unable to assess the situation independently and continues in a state of apathy that needs external motivation. Depending on the severity of GUI this external motivation has been achieved through nurturing, reasoning, cajoling, ridiculing, physical

intervention and even actual violence. Strassman [11] points out from his own experience that two things seemed to save the man close to 'apathy death': getting him on his feet doing something, no matter how trivial, and getting him interested in some current or future problem. Clearly, anything involving the future implies a functioning PFC and executive function is necessary to adapt to a new environment, develop coping skills [66], plan for the future (hope) and establish goal-directed behaviour.

Motivation is essential for coping. When a trauma victim in a camp became apathetic or was dying, responsibility for him was assumed by others in the group who had a special connection to him which they could use to snap him out of apathy or to provide comfort if he was dying. This maternal approach did not always work and more direct, forceful tactics were employed to overcome apathy and resignation. In one case such 'therapy' consisted of kicking the man until he was mad enough to get up and fight [2]. Clearly, such external actions worked. As one PoW in Vietnam said of his forceful treatment, 'As a result, I slowly began to pull out of my fatalistic resignation. […] We all knew that if we didn't get our minds off dying that any one of us would be next' [3]. A prisoner in a concentration camp later described his recovery from GUI, 'I was overcome by general apathy… nothing interested me and I did not react to outside stimuli, I did not wash even when I had the chance to do it, did not even feel hunger. I lived as in a dream. I owe it entirely to my friends that I recovered from this… They organised some water, stripped of my clothes and washed [me]. Since that moment something happened to me, it was simply an electric shock! I became a normal prisoner, wishing to survive at any cost' [67]. Similarly, in Jamestown in 1609 it was reported that amongst early settlers in America who were overcome by isolation and despair recovery could be achieved by forced activity usually through a forceful leader and, '…most strange of some 150, that had they not beene forced *nolens volens* perforce to gather and prepare their victuall they would all have starved' [68]. It is recognised that intentional self-generated aspects of behaviours (willed actions) are controlled differently from routine externally

triggered actions, so the action mechanisms may be intact but the initiator may be dysfunctional. The external motivator bypasses the internal initiator to trigger motivated actions [46, 69].

Physical activity is known to increase DA production in rats, monkeys and humans [70] and it is possible that increased activation amongst GUI victims, whether enforced or voluntary, would also boost DA production. This DA increase contributes to the modulation of both the NAc, increasing motivation and goal-directed behaviour, and the PFC, increasing cognitive functioning leading to an appraisal of the situation as being at least partially controllable. This, in turn, leads to a further increase in DA production in the NAc. Recovery is ensured when extrinsic motivation is replaced with intrinsic motivation. As pointed out by Des Pres [14], the purpose of action in extremity is to keep life going.

In the initial phase of a self or assisted recovery from GUI a person begins to make his or her first adjustment to the new world in which they find themselves and where old standards may no longer exist. As described by Lunden [25] and Newman [71], the survivor 'licks his wounds and wakes up', begins to take an interest in his surroundings and tries to make his environment as habitable as possible. Once more men begin to shave, and to undress to sleep. He attempts to control his situation and to impose a kind of orderliness on his effects. Some people accepted the fact that there were aspects of their life that they could not control and chose to focus their energies on what they could regulate [72] suggesting that even partial control of a stressful situation was beneficial in overcoming GUI. It is interesting that Des Pres [14], observing an increasing capacity for adapting to conditions in the concentration camps noted, that when the moment of turning finally came, it was attended by a strong sensation of choice. That sensation of choice indicates a reversal of mental defeat and the reimposition of some personal control over the situation which is a key factor in recovery. This is also comparable with aboulic patients who, when externally

motivated, feel that they are acting freely and voluntarily [73] which may assist in the transition from extrinsic motivation to the re-establishing of intrinsic motivation.

This description is consistent with increased DA production and suggests a return of goal-directed behaviour, an assumption of a future and a perception that some control can be imposed over a nonetheless continuing traumatic and stressful situation. With this recovery comes hope and hope can be viewed as a reward based behaviour that, in turn, implies DA modulation. Furthermore, reports show that if an individual is recovered from this state then he or she rarely reverts suggesting a more permanent recovery in functional DA levels. It appears, therefore, that observed instances of people overcoming GUI, and methods for coping in stressful situations, are allied with mechanisms of DA production.

Conclusion: A conceptual theory for 'Give-Up-Itis'

A general theory for the cause and progression of 'give-up-itis' is presented in which it is proposed that GUI is the clinical expression of mental defeat; in particular, it is a pathology of a normal, passive coping response.

GUI follows psychogenic trauma and progresses from an initial withdrawal response through a spectrum that includes apathy, conditions comparable to aboulia and psychic akinesia before concluding in psychogenic death. The progressive demotivation and executive dysfunction observed during GUI have clinical parallels suggesting frontal-subcortical dysfunction consequent upon impairment of the PFC-basal ganglia system particularly the dorsolateral prefrontal circuit and the anterior cingulate circuit. GUI is circuit specific behaviour that results from abnormal activity in an otherwise intact system in which traumatic shock causes the neurochemical environments of the PFC and NAc to disequilibrate.

Given its role in both motivation and modulating stress reactions the most probable neurotransmitter candidate in GUI is dopamine. Stressful situations that can be controlled or avoided result in an increase in DA production in the PFC and NAc producing active coping behaviour. However, stressful situations that cannot be controlled or avoided cause a decrease in DA production in the NAc that results in passive coping behaviours such as emotional withdrawal from the stressor, while further decreases in NAc DA is associated with coping failure [56]. It is this perception that the situation is inescapable that appears to be a key factor in GUI and one that is modulated by differential DA release in the PFC and NAc.

Motivation, higher order cognition and executive function are necessary to establish goal-directed behaviours, plan for the future and adapt to a new environment. These processes are recovered when the GUI victim appraises that he or she has some control over his or her situation and along with recovery comes a desire for order, cleanliness and hope in a future. If recovery does not occur then the victim progresses to the final Stage V GUI which can be considered as a pre-stage to psychogenic death characterised by a brief and mild resurgence in executive function, auto-activated goal-directed behaviour, motoric activity, hedonia, speech initiation and recovery from cognitive inertia or 'empty mind' syndrome.

It is speculated that progressive GUI is consequent upon DA depletion in the anterior cingulate circuit, particularly in the NAc, so a return of apparent goal-directed behaviour suggests a slight but functional increase in DA levels. The question arises as to why a postulated increase in DA often does not lead to further recovery from GUI but rather heralds psychogenic death. A possible answer may lie in the context of the traumatic situation with the GUI victim appraising that death actually provides the means of control over the stressful and inescapable situation in which he or she finds him or herself. In other words, the continuing traumatic stress can be avoided through the strategic use of death; that death itself is perceived as a natural coping behaviour.

Conflict of interest statement

The author declares that he has no conflict of interest.

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Normal behaviour	Stage I withdrawal	Stage II apathy	Stage III aboulia	Stage IV akinesia	Stage V psychogenic death
Routine, adaptive and motivated, goal-directed behaviour. Ability to think ahead and plan.	Withdrawal, impaired initiative, reduced activity. Cognitive function intact. Speech reduced but coherent. Self-motivation diminished but possible.	Apathy, inertia, impaired initiative even for personal hygiene and dress. Cognitive function intact. Anhedonia. Intrinsic motivation possible but greater reliance on extrinsic motivators.	Aboulia, loss of emotional response, initiative and willpower. Cognitive function diminished but intact. Ceases washing and caring for personal hygiene. Loss of intrinsic motivation. Extrinsic motivation still possible.	Akinesia, lack of response to external stimuli, even to pain. General cognition intact but signs of executive impairment. Ceases washing and caring for personal hygiene, often ceases eating. Regression to infantilism. Intrinsic motivation absent, no response to external motivators.	Psychogenic death. Further regression to infantilism. Basic cognitive function lucid up to the end. Speech still intact and coherent. Apparent return of hedonia. Death.

Figure 1. Conceptual framework for progression of ‘give-up-itis’ syndrome