Hypothesis

Syndrome E

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The transformation of groups of previously nonviolent individuals into repetitive killers of defenceless members of society has been a recurring phenomenon throughout history. This transformation is characterised by a set of symptoms and signs suggesting a common syndrome—Syndrome E. Affected individuals show obsessive ideation, compulsive repetition, rapid desensitisation to violence, diminished affective reactivity, hyperarousal, environmental dependency, group contagion, and failure to adapt to changing stimulus-reinforcement associations. Yet memory, language, planning, and problem-solving skills remain intact. The main risk factors are male sex and age between 15 and 50. A pathophysiological model—"cognitive fracture"—is hypothesised, where hyperaroused orbitofrontal and medial prefrontal cortices tonically inhibit the amygdala and are no longer regulated by visceral and somatic homeostatic controls ordinarily supplied by subcortical systems. It is proposed that the syndrome is a product of neocortical development rather than the manifestation of a disinhibited primitive brain. Early recognition of symptoms and signs could lead to prevention through education and isolation of affected individuals.

Repeatedly throughout history, groups of individuals, usually young men, have violently attacked other members of society, often with the approval of, or encouragement from, those in authority. The victims are usually defenceless and are no direct threat to their attackers. Some of the notable manifestations of the phenomenon in this century are the killing of Armenians by Turks in 1915–16, of European Jews during World War II, of Cambodians during the Pol Pot regime in the 1970s, and the ethnic killings in Rwanda in the 1990s. Civil strife, extreme conditions, and ethnic conflicts have often had a role in these events, much as poverty and lack of hygiene lead to outbreaks of infectious disease. Yet these events would not have happened without a distinct transformation in the behaviour of individuals. The uniformity and repeating nature of this transformation suggests a common syndrome affecting individuals for which I propose the term “Syndrome E”.

Symptoms and signs

Repetitive acts of violence The hallmark of the syndrome is the perpetration of repetitive acts of violence. The individual engages in stereotyped repetition of aggression, characterised by compulsion to spare none of the victims.1,2

Obsessive ideation Individuals are obsessed with a set of beliefs, often directed against a minority group. The combination of repetitive stereotyped acts accompanied by recurring ideation resembles the symptoms and signs of obsessive-compulsive disorder. Metaphors such as “cleansing” are often used to justify violence.3,4

Perseveration Individuals show stereotyped behaviour that perseverates in the face of changing circumstances, even when it is no longer appropriate for the situation and may jeopardise the individual’s interests.5 This behaviour reflects failure to adapt to changing stimulus-reinforcement associations.4

Diminished affective reactivity Much of the violence perpetrated by individuals is carried out, not in battlefield frenzy nor in a burst of emotion, but with flat effect.

Hyperarousal (Rausch) The repetitive nature of violent acts often invokes a sense of Rausch (elation) according to the number of victims and the magnitude of destruction.5

Intact language, memory, and problem-solving skills Individuals affected by the syndrome usually appear intellectually sound and remain intact in cognitive domains such as language, memory, and the ability to plan and solve problems.

Rapid habituation In the early stages of the syndrome, there is rapid habituation to acts of violence. While some report strain with initial homicidal activity, especially toward children and women, most individuals undergo desensitisation within a relatively short time.6

Compartmentalisation Individuals conduct activities calling for seemingly conflicting cognitive states. They may lead a normal family life, while in parallel engaging in killing of families.6

Environmental dependency Behaviour is abnormally dependent on environment and context, which determine the borders of the behavioural compartments described above. Obedience to authority and dependency on group support are examples.

Group contagion The group environment is necessary for maintenance of the syndrome and for its propagation. Most individuals in the group respond uniformly to sets of stimuli, and the responses of individuals in the group serves as stimuli for other individuals.

Several of the signs and symptoms of Syndrome E are evident in the behaviour of the individual shown in the figure taking aim at a woman and child. The circumstances indicate that the individual had taken part repeatedly in similar acts. The act of killing in front of a
photographer is an example of diminution of affective reactivity, but also suggests elation associated with the killing. Compartmentalisation is suggested by the mailing of this and other similar photographs by German soldiers along with accounts of the events to their families at home.1

**Differential diagnosis**

Syndrome E is a specific set of symptoms and signs. It is not a general syndrome of human aggression and should not be confused with the behaviour of individuals who carry out repetitive homicidal acts alone. These individuals constitute a very small proportion of the population, and they often have a history of psychopathology. Neither should Syndrome E be confused with the usual manifestations of war or group combat. These conflicts often lead to atrocities, carried out by individuals in the frenzy of battle. Such behaviour, however, lacks most of the features described above and is characterised by inverse symptomatology: emotional reactivity rather than dulling, and incidental, sporadic violence rather than perseveration and systematic repetition.

**Pathophysiology**

**Prefrontal cortex**

Most features of the syndrome can be found in disorders involving prefrontal cortical systems and their subcortical connections. The prefrontal cortex has three major systems—dorsolateral prefrontal cortex, orbitofrontal cortex, and medial prefrontal cortex. The dorsolateral prefrontal system appears relatively unaffected in individuals with the syndrome since they are capable of planning, problem solving, language, and working memory. Obsessive ideation and repetitive acts of violence suggest orbitofrontal hyperkinesia, similar to that found in patients with obsessive-compulsive disorders.11 The motivation and elation accompanying repetitive homicidal acts suggest hyperactivity of the medial prefrontal cortex. This elation may be similar to drug-induced hyperarousal syndromes such as that induced by cocaine seen in rhesus monkeys and human beings.12 The medial prefrontal cortex is a major site of activation associated with compulsive self-administration of addictive drugs.13

“Cognitive fracture”

In common with patients with ventromedial prefrontal dysfunction, individuals with Syndrome E cease to generate emotions appropriate to the images conjured by certain categories of situation and stimuli. Responses of the prefrontal cortex fail to arouse the autonomic, musculoskeletal, and endocrine substrate of emotion; nor are these responses regulated by somatic and visceral homeostatic controls ordinarily supplied by subcortical systems.15 The prefrontal cortex becomes functionally disconnected from the lower neural centres—a state that is here termed “cognitive fracture”.

**Amygdala**

The primary pathology underlying cognitive fracture may be in the interaction between the amygdala and prefrontal cortex. The amygdala has extensive connections with the orbitofrontal and medial prefrontal regions and has robust output to the hypothalamus and brain-stem nuclei, whereby it is presumed to regulate the autonomic, musculoskeletal, and endocrine substrates of emotions.15 Studies in animals suggest that the amygdala is tonically inhibited by prefrontal activation.16 The combination of cortical hyperarousal and diminished affective reactivity in Syndrome E may be due to hyperactivity of orbitofrontal and medial prefrontal cortices shutting off the amygdala and impairing its ability to regulate emotion and impart species-specific meaning to stimuli. Affected individuals then simultaneously perceive their victims as living and non-living, but at the same time, by mechanical repetition and compulsion, they approach a state of automation, with intrinsic uncertainty about their own sense of living.1 Despite the rapidity of the behavioural change in Syndrome E, its expression is probably preceded by a longer learning process. Individuals undergo implicit emotional learning, resulting in an attitude toward their victims that is similar to phobias in patients or fear-conditioning in rats. These deeply rooted attitudes are resistant to extinction. Such extinction depends on output from the medial prefrontal cortex to the amygdala,13 which is impaired in Syndrome E.
Neocortical development vs subcortical disinhibition

The symptoms and signs of Syndrome E are sometimes viewed as animal-like, and attributed to a phylogenetically older “visceral brain” released from the inhibitory control of the neocortex. However, with the possible exception of observations in higher nonhuman primates,17 animals do not show the signs of the syndrome. The syndrome is more logically viewed as a product of neocortical development rather than of a disinhibited primitive brain. The hypothesis of cognitive fracture affecting a large number of individuals suggests vulnerability in the human neuraxis at the interface between the rapidly evolved prefrontal cortex and the phylogenetically older subcortical nuclei.

Testing the hypothesis

It is likely that recovery from Syndrome E is accompanied by hysterectomy—the persistence of abnormalities beyond expression of the syndrome. Long-term study of affected individuals compared with that of unaffected members of the same group and with unaffected members of other groups, could be informative.

Affective reactivity

Compared with control groups, individuals with Syndrome E would be expected to show diminution of changes in skin conductance, facial electromyography, and potentiation of startle reflex responses when presented with affective stimuli.14,16 They would not show the facilitation of memory for stimuli with negative emotional valence seen in unaffected individuals. Nor would they show selective decrease in memory for such stimuli seen with administration of beta-adrenergic-receptor antagonists.18 In common with patients with ventromedial prefrontal dysfunction, these individuals would not choose advantageously or generate anticipatory skin-conductance responses whenever they ponder a risky choice in gambling experiments.19

Perseveration

Individuals with Syndrome E should perform poorly on orbitofrontal tasks, such as rapid alteration of stimulus-reinforcement associations, but they should not differ from controls in performances on tests of dorsolateral frontal function, such as Wisconsin Card Sorting.4

Prefrontal hyperarousal

In disorders such as schizophrenia and epilepsy, there is hypermetabolism and increased blood flow during the acute episodes but opposite changes after these episodes.20 Similarly, it would be expected that individuals with Syndrome E will show acute hyperfrontality during outbreaks, but long-term hypofrontality as measured by positron-emission tomography, single-photon emission computed tomography, and event-related potentials. Violent behaviour seen in youth gangs share with Syndrome E compulsive repetition, diminished affective reactivity, hyperarousal, and group contagion. Study of gang members may be more feasible than studies involving full-blown manifestations of Syndrome E.

Prevention

Isolation of individuals with Syndrome E may offer hope of containing an outbreak, because the syndrome will not persist or propagate without contact with other individuals at risk or with potential victims. Prompt diagnosis would be of paramount importance as prevention may be effective only in the early stages. The signs and symptoms of the syndrome should be made widely known. Individuals in most societies know that a constellation of high fever and coughing may indicate pneumonia. In the same sense, people might become aware that symptoms of an emerging obsessive ideology, hyperarousal, diminished affective reactivity, and group-dependent aggression directed at members of other subgroups may signify Syndrome E.

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References