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CRITICAL REVIEW

Neuropsychological and neuropathological sequelae of cerebral anoxia: A critical review

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Abstract

Fifty-eight studies of the neuropathological and neuropsychological outcomes of cerebral anoxia were reviewed. Neuropathological reports were examined for the variety, extent, and specificity of lesions resulting from an anoxic event. While most attention has focused on damage to the hippocampus following anoxic brain injury, the review indicated that watershed cerebral cortex and the basal ganglia were both more frequently damaged than the hippocampus. The hippocampus was the sole affected structure in only 18% of reported cases. Neurological, neuropsychological and psychiatric studies were analyzed. Of 67 individual case reports, a memory disturbance was documented in 36 (54%), but a memory disturbance without report of additional cognitive deficits occurred in only 13 (19.4%). Changes in personality and behavior were noted in 31 (46.2%). Visuospatial or, less frequently, visual recognition problems were noted in 21 individual cases (31.3%) reviewed. Memory deficits were found in all 14 group studies reviewed, while in 9 papers changes in behavior or personality were also documented. Six studies also reported visuospatial deficits. Careful reading of the literature reveals a range of cognitive and behavioral changes that reflect very well the neuropathological outcomes of anoxic episodes. (*JINS*, 2000, *6*, 86–99.)

Keywords: Cerebral anoxia, Cardiac arrest, Cognition disorders

INTRODUCTION

One of the earliest studies of anoxic brain injury was entitled *Personality Disintegration Incident to Anoxia: Observations With Nitrous Oxide Anaesthesia* (Fletcher, 1945). Reporting on 8 cases of anoxia from nitrous oxide poisoning, Fletcher noted persisting defects of judgement, loss of insight, apathy, indifference, and restlessness, in addition to deficits in attention and memory in all 8 patients. In a similar vein, Steegman (1951) considered "silly and childlike behavior" and "peculiar emotional changes" to be the primary defects in cerebral anoxia.

In spite of these perspicacious early insights into changes in behavior and personality resulting from anoxic episodes, it has been the disturbance to memory function in such patients that has attracted the most attention. Over successive decades cerebral anoxia has come to be identified principally as one of the most significant causes of an isolated amnesic syndrome (Berlyne & Strachan, 1968; Cummings et al., 1984; Medalia et al., 1991; Muramoto et al., 1979; Volpe & Hirst, 1983; Whiteley, 1958). At the same time, since the seminal study by Scoville and Milner (1957) an intense interest has developed in the role of the hippocampus, one of the structures vulnerable to anoxic injury, in memory. A small number of cases with anoxic brain injury, damage to the hippocampus and an amnesic syndrome without significant accompanying cognitive deficits has been published (Cummings et al., 1984; Press et al., 1989; Volpe & Petito, 1985; Zola-Morgan et al., 1986). Interest in these cases has derived from their being instances of an amnesic syndrome associated with pathology of the hippocampus rather than from their being primarily cases of anoxic brain injury.

An inadvertent outcome of this focus on the amnesic syndrome which can sometimes result from damage to the hippocampus in anoxic events, is that this has come to be regarded as the prototypical neuropathological and neuropsychological outcome of cerebral anoxia. Thus, in a chapter on amnesic disorders in a leading neuropsychological textbook, Bauer et al. (1993) noted that support for the importance of the hippocampus in memory has been derived from the permanent amnesia that follows hypoxic–ischemic encephalopathy in humans. The same chapter refers to the loss of neurons in the hippocampus following cardiac arrest

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in the case of Zola-Morgan et al. (1986). There is no other reference to neuropsychological outcomes from anoxia in this important neuropsychology text.

It would be quite incorrect for us to argue that an isolated amnesic syndrome with accompanying pathology solely affecting the hippocampus does not occasionally occur following an anoxic event (Cummings et al., 1984; Muramoto et al., 1979; Petito et al., 1987; Volpe & Hirst, 1983; Zola-Morgan et al., 1986, 1992). However, the mechanisms and distribution of neuronal damage in cerebral anoxia are such as to render lesions specific to the hippocampus possible, but unlikely. This paper presents a review of the literature on cerebral anoxia. It aims to demonstrate the patterns and diversity in reported outcomes from an anoxic etiology and the extent to which those outcomes accord with the known neuropathology of this condition.

Pathophysiology of Cerebral Anoxia

The human brain has a constant requirement for oxygen to meet energy demands. Although the brain receives a significant portion (about 15%) of the cardiac output, it does not store oxygen (Kuroiwa & Okeda, 1994; White et al., 1984). When oxygen delivery is disrupted, a series of cerebral homeostatic and vascular mechanisms is activated, directed toward maintaining oxygen supply (Cohen, 1976; Strandgaard & Paulson, 1984). This autoregulation maintains cerebral blood flow against abrupt blood pressure change within a certain range (about 50–150 mm Hg) and maintains delivery and utilization of oxygen despite fluctuations in supply (Cohen, 1976; Michael, 1973). Therefore, even though the brain does not store oxygen, oxygen deprivation must be sustained in order to render cerebral autoregulatory mechanisms ineffectual and for the brain to become injured. A period of longer than 4 to 8 min is said usually to produce cerebral infarction and disseminated cell death (Bigler & Alfano, 1988; Caronna, 1979; Cohan et al., 1989; Cohen, 1976; Strandgaard & Paulson, 1984; White et al., 1984).

Because the final common pathways to oxygen deprivation, irrespective of the nature of the precipitating event, are both reduced oxygen content in the blood and reduced blood flow to the brain (Bigler & Alfano, 1988; Moody et al., 1990), "anoxia" or "hypoxia" are frequently used synonymously with "ischemia," sometimes as the hybrid term "hypoxia–ischemia" (Caronna, 1979; Ginsberg et al., 1976; Schurr & Rigor, 1992; Volpe & Hirst, 1983). In this paper "anoxia" is used to refer to a reduction in the supply or utilization of oxygen and metabolic substrates, irrespective of the precipitating event. The literature on carbon monoxide poisoning was not systematically reviewed here because both the mechanisms and the sites of damage are considered to differ significantly from other causes of cerebral anoxia (Meredith & Vale, 1988; Remick & Miles, 1977).

The mechanisms by which anoxic damage is produced are both complex and diverse. They comprise a cascade of time-dependent alterations in neuronal function, metabolism and morphology (Haddad & Jiang, 1993; Pulsinelli et al., 1982). Hypoxic damage to central neurons is produced acutely by the release of excitatory neurotransmitters, which leads to an influx of sodium, cell swelling and cell injury (Hansen, 1985; Kjos et al., 1983; Rothman & Olney, 1986). Longer-term damage is related to both an increase in neuronal excitability (Choi, 1990) resulting in an influx of calcium (Ascher & Nowak, 1987; Gibson et al., 1988; Haddad & Jiang, 1993; Hansen, 1985; Siesjo, 1981; White et al., 1984) and to the formation of oxygen free radicals. These are unstable molecules that, because of their configuration involving an unpaired electron, are extremely reactive and are liable to transform many molecules, thus causing cell injury (Haddad & Jiang, 1993; Maiese & Caronna, 1989; Schurr & Rigor, 1992; Siesjo, 1981).

In addition to these primary mechanisms, there are secondary sources of cerebral injury in anoxic conditions. There is evidence that neurons themselves may be able to survive much longer periods of hypoxia than usually thought (White et al., 1984) but that when the general circulation is restored, cerebral circulation does not always respond adequately. It has been suggested that the cerebral microcirculation may not be able to purge the metabolites accumulated during the period of hypoxia, and that the capillaries and small arterioles may be so affected by focal or widespread areas of brain edema that they do not regain normal flow (the phenomenon of "no-reflow"; Ames, 1973; Ginsberg & Myers, 1972; Miller, 1984; Myers, 1979). While there may be substantial hyperperfusion initially, there seems to be a progressive increase in cerebral small-vessel resistance resulting ultimately in perfusion rates too low to support neuronal viability in the cerebral cortex (White et al., 1984). It is not clear whether this phenomenon only occurs in brains that have already suffered primary irreversible hypoxic damage, since a significant degree of tissue damage is sustained in the absence of impaired reperfusion (Brierley & Graham, 1984; Welsh, 1985). The mechanisms by which hypoxic damage is produced are thus both complex and diverse. These factors, together with the variability inherent in any specific episode of oxygen deprivation can lead to highly variable pathological outcomes (Myers, 1979).

Neuropathology of Cerebral Anoxia

What determines the distribution of pathology in cerebral anoxia? Two principal factors have been invoked to explain the principle of "selective vulnerability" (Brierley & Graham, 1984), on the basis of which anoxic cerebral injury occurs. The first concerns the distribution and disposition of cerebral blood vessels such that those portions of the supply territory that lie in the fringes of supply of the major cerebral arteries are the first to experience reductions in blood flow (Brierley & Graham, 1984). Second, the specific metabolic and biochemical properties of the structures involved are such that the higher the metabolic demand of a given area the more likely it is to be affected by oxygen deprivation (Moody et al., 1990; Myers, 1979).

In addition to these general principles, the mechanisms of vulnerability of different cell groups within the most commonly affected areas are also differentiated. For example, striatal neurones are sensitive to increased dopaminergic activity (Calabresi et al., 1995; Globus et al., 1987), while in the hippocampus vulnerability to oxygen deprivation appears to be related to the action of excitatory amino acid neurotransmitters such as glutamate and aspartate, which initiate the release of intracellular calcium resulting in neuronal death (Kuroiwa & Okea, 1994, but see Moody et al., 1990). Finally, it has been shown that different brain regions respond over different time courses. Necrosis in the basal ganglia and cerebral cortex appears shortly after cardiac arrest, while ischemic change in the hippocampus is markedly delayed, not appearing until 2 to 3 days following the event (Kuroiwa & Okeda, 1994; Petito et al., 1987; Pulsinelli, 1985; Pulsinelli et al., 1982). Although the principle of selective vulnerability dictates that certain brain regions will be more susceptible in anoxia, these additional factors, together with the variability inherent in any specific episode of oxygen deprivation, can lead to highly variable pathological outcomes (Myers, 1979).

METHODS

The papers under review were found by means of a computerized Medline search of the English language literature from January 1966 to May 1998. This was followed by extensive hand searching using the references cited in the first round of the search as a starting point. The search thus represents a more extensive review of the relevant literature than has ever previously been published. Some studies reported detailed neuropathological and neuropsychological data and were considered in both categories. Neuropathological studies as well as studies of structural imaging were examined for the variety, extent and specificity of lesions occurring in the hippocampus and in other brain regions in consequence of an anoxic event. Some of the neuropathological reports aimed to document the neuropathological sequelae of anoxic events (see, for example, Adams et al., 1966) while others aimed to demonstrate focal pathology associated with a specific neuropsychological outcome (see, e.g., Cummings et al., 1984). The analysis conducted by the authors was intended to enable a comparison of studies irrespective of their specific focus. To this end, neuropathological reports were analyzed in terms of whether, and in which regions, cell loss was reported. To enable comparison between such varied studies, cortical areas were subdivided into four regions: *cortex-unspecified; anterior cortex; posterior cortex*; and *white matter*. Based on those areas identified by Brierley and Graham (1984) as liable to be affected, the subcortical areas selected were hippocampus, striatum, pallidum, and thalamus.

Neurological, neuropsychological and psychiatric reports were analyzed for descriptions of cognitive, personality, or behavioral changes in addition to memory deficits. These studies also differed in their orientation in that some were directed towards documenting outcomes from anoxic episodes (see, e.g., Grosswasser et al., 1989) while others were more concerned with a specific outcome, such as an amnesic syndrome, which happened to result from cerebral anoxia (see, e.g., Cummings et al., 1984; Muramoto et al., 1979; Volpe & Hirst, 1983). Again, in order to enable some comparison between studies, whether or not a change in individual patients was observed in any of the four categories of cognitive function most commonly investigated—memory; personality, behavior, or executive function; visuoperceptual function; and language—was recorded. The present authors were thus reliant on the descriptions and methods of the original researchers for this categorization, although actual test results as well as case descriptions were examined.

RESULTS

The Distribution of Pathology in Cerebral Anoxia

Of 43 cases reviewed in 10 neuropathological studies of cerebral anoxia, 32 cases had cell loss in the cerebral cortex. Thirty-one had lesions in either the pallidum or the striatum or both (see Tables 1 and 2). So, although specific hippocampal changes have been examined the most extensively in this condition (see, e.g., Zola-Morgan et al., 1986), the hippocampus was not the most frequently damaged structure, with 30 cases having hippocampal damage. The hippocampus was the sole affected structure in 8 of 43 cases (Meyer, 1956; Rempel-Clower et al., 1996; Volpe & Petito, 1985; Zola-Morgan et al., 1986). Four cases had damage in the basal ganglia but not in the hippocampus (Adams et al., 1966; Ginsberg et al., 1976; Petito et al., 1987). In a further 6 cases there was significant change in the basal ganglia with minimal cell loss in the hippocampus (Adams et al., 1966; Volpe & Petito, 1985). Fourteen of the 25 cases in which the thalamus was examined showed damage in that structure.

Structural Imaging of Cerebral Anoxia

Eleven computed tomography (CT) and magnetic resonance imaging (MRI) studies were examined, involving a total of 90 patients. Structural imaging was typically found to be normal in the early postanoxic period (Volpe & Hirst, 1983), but abnormalities were evident as early as 24 to 48 hr following a prolonged anoxic episode (Kjos et al., 1983; Tippin et al., 1984).

Of the 90 cases in the studies reviewed, 40 showed a diffuse effect involving edema or atrophy of the cerebrum. Thirty cases demonstrated hypodensities in the cerebral and cerebellar cortices. Changes in density or signal intensity in the caudate and lentiform nuclei were observed in 20 cases while 3 cases had marked changes in the thalamus. Most remarkable was that only 2 cases in two separate studies

Table 1. Analysis of neuropathological studies of hypoxic patients since 1956 showing cortical brain regions affected

Author (date)	Case	Cortex–unspecified	Cortex–anterior	Cortex–posterior	White matter
Meyer (1956)	1	++			
	2	+			
	3	++			
	4	++			
	5	++			
	6	++			+
Brierley & Cooper (1962)	1		+		+
Adams et al. (1966)	1		++	++	++
	2		++	++	–
	3		++	++	+
	4		++	++	++
	5		+	++	minor
	6		–	++	–
	7		+	++	–
	8		+	++	–
	9		++	++	+
	10		+	++	–
	11		+	++	minor
Ginsberg et al. (1976)	1		–	–	++
	2				++
	3		–	–	++
Cummings et al. (1984)	1		minor	–	–
Volpe & Petito (1985)	1		–	–	–
	2		–	–	–
Zola-Morgan et al. (1986)	1		–	+	–
Petito et al. (1987)	1		+	n	n
	2		++	o	o
	3		+	t	t
	4		++		
	5		+	e	e
	6		+	x	x
	7		++	a	a
	8		++	m	m
	9		+	i	i
	10		++	n	n
	11		++	e	e
	12		+	d	d
	13		++		
	14				++
Revesz & Geddes (1988)	1		++	++	–
Rempel-Clower et al. (1996)	1		–	–	–
	2		–	+	–
	3		–	–	++

Note. Minor = only very mild cell loss detected, + = mild–moderate cell loss, ++ = severe cell loss.

were reported to have isolated hippocampal abnormalities (Press et al., 1989; Takashi et al., 1993). One of these studies (Press et al., 1989) was specifically directed towards investigating the amnesic syndrome associated with hippocampal abnormalities. The 3 cases in this report were therefore specifically selected, but only 1 of them was known to have an anoxic etiology.

Two additional studies of the memory disorder associated with anoxic episodes by Hopkins et al. (1995b, 1995c) compared the performance of 11 known anoxic patients with 10 age-, sex- and education-matched controls. These patients were chosen specifically because it was argued that in anoxia the brain damage may be more selective than in other pathologies associated with amnesia. While the mean

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Table 2. Analysis of neuropathological studies of hypoxic patients since 1956 showing subcortical brain regions affected

Author (date)	Case	Hippocampus	Basal ganglia striatum	Basal ganglia pallidum	Thalamus
Meyer (1956)	1	++	++	+	+
	2	+	–	–	–
	3	++	++	++	–
	4	++	+	+	+
	5	+	++	++	++
	6	++	–	++	+
Brierley & Cooper (1962)	1	minor	–	–	++
Adams et al. (1966)	1	minor	patchy	–	minor
	2	minor	+	–	–
	3	+	++	–	++
	4	–	++	–	++
	5	–	++	++	minor
	6	minor	++	–	++
	7	–	–	–	++
	8	minor	+	–	++
	9	–	++	++	++
	10	+	+	+	++
	11	minor	–	–	++
Ginsberg et al. (1976)	1	–	–	++	–
	2	++	++	–	–
	3	–	–	–	–
Cummings et al. (1984)	1	++	–	–	minor
Volpe & Petito (1985)	1	+	–	–	minor
	2	+	–	–	minor
Zola-Morgan et al. (1986)	1	++	–	minor	–
Petito et al. (1987)	1	–	++	n	n
	2	minor	++	o	o
	3	+	++	t	t
	4	minor	++		
	5	+	+	e	e
	6	+	minor	x	x
	7	minor	++	a	a
	8	+	++	m	m
	9	++	+	i	i
	10	++	++	n	n
	11	++	++	e	e
	12	++	++	d	d
	13	++	++		
	14	++	++		
Revesz & Geddes (1988)	1	++	++	++	++
Rempel-Clower et al. (1996)	1	++		+	minor
	2	++			
	3	++			

Note. Minor = only very mild cell loss detected, + = mild–moderate cell loss, ++ = severe cell loss.

area of hippocampus was shown to be smaller in this group of anoxic patients, the only extrahippocampal areas reported were in the temporal lobes (Hopkins et al., 1995b). As has already been demonstrated isolated hippocampal injury is an unusual outcome of cerebral anoxia. Hippocampal abnormalities, whether in isolation or not, have not always been detected in anoxic patients, even when coronal slices have been specifically examined (Hori et al., 1991).

Cognitive Sequelae of Anoxic Episodes

Two hundred and ninety-nine cases, in 36 papers that examined cognitive or behavioral changes in detail, were analyzed in all (see Appendix). Three additional papers, which were not amenable to numerical analysis because of the method of reporting of cognitive outcomes, were also considered for their important historical perspective (Fletcher,

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1945; Meyer, 1956; Steegman, 1951). Articles that expressed outcomes in terms of global neurological as opposed to neuropsychological status were excluded from the analysis.

Twenty-two of the 36 papers reviewed provided detailed information about the cognitive status of individual patients. In 14 papers only group data were reported, without analysis of the profiles of individuals within the group. Because of the difficulty comparing the results of these different approaches to data analysis, each paper was assigned to the category of an individual or a group study and each category was reviewed separately. It is worth noting again that often the studies reviewed were undertaken with the intent of exploring specific neuropsychological phenomena rather than outcomes from anoxia *per se*.

Individual Case Studies

Sixty-seven detailed individual case reports in 22 papers were reviewed. Methods of assessment ranged from interview and observation (Allison, 1956; Collins & Jacobson, 1990; Reich et al., 1983) to formal and extensive neuropsychological assessment (see, for example, Milner et al., 1991; Hopkins et al., 1995a). In most studies neuropsychological assessment comprised at least the Wechsler Adult Intelligence Scales (WAIS) or Wechsler Adult Intelligence Scales–Revised (WAIS–R) and the Wechsler Memory Scale (WMS) or Wechsler Memory Scale–Revised (WMS–R). Additional neuropsychological testing was extremely varied. Testing of executive function, if formally assessed, was limited to the Wisconsin Card Sorting Test, the Halstead Category Test and the Benton test of verbal fluency (Hopkins et al., 1995a; Volpe & Hirst, 1983). Language assessment was usually minimal. Most frequently the Token Test of comprehension and the Boston Naming Test were used (see, for example, Volpe & Hirst, 1983) but exceptions are discussed below.

Amnesia

An amnesic syndrome was reported in 36 of 67 cases (54%), while memory disturbance without accompanying cognitive change was identified in 13 (19.4%) of them (Allison, 1956; Cummings et al., 1984; Hopkins et al., 1995a; Medalia et al., 1991; Muramoto et al., 1979; Rempel-Clower et al., 1996; Volpe & Hirst, 1983; Whiteley, 1958). In all cases an anterograde memory loss was recorded. A retrograde memory impairment was documented in only 4 cases. Muramoto et al. (1979) reported the case of a 59-year-old carpenter in whom "pure memory loss" occurred following inhalation anesthesia. While his capacity to register new information was severely impaired, he made no errors in judgement in relation to his trade and there was no other evidence of cognitive decline. Volpe and Hirst (1983) described an isolated amnesic syndrome in 3 cases. The amnesia was said to be characterized by intact registration, severely depressed free recall, less depressed recognition memory, and greater than normal susceptibility to interference. In each case performance on the Wechsler Memory Scale was compared with WAIS Full Scale IQ (FSIQ) with discrepancies ranging from 29 to 45 scaled points. Performance on the Wisconsin Card Sorting Test and on a test of verbal fluency was normal in all 3 patients. One of the three was described as being "unconcerned, apathetic and flat" in the acute phase, defined as the first few months after injury, but subsequently his family members reported "some return of the 'personality' they used to know." These observations were explained in terms of an "acute phase," comprising confusion associated with unconcerned or apathetic mood, followed by a "stable phase" in which personality changes were thought to have resolved.

Volpe and Hirst (1983) and Volpe et al. (1986) argued that the relative difference between recognition and recall performance was greater for anoxic patients than that for controls (Volpe et al., 1986). However, such a discrepancy between recognition memory and free recall has not always been observed in anoxic patients. Cummings et al. (1984) reported a 53-year-old man who sustained a cardiopulmonary arrest and whose inability to form new memories was not helped by prompting, cues or repetition. Corkin et al. (1985) found no difference between recognition memory and free recall in a study that compared amnesics of different etiologies including cerebral anoxia.

More recently Hopkins et al. (1995b, 1995c) have explored the specific characteristics of the memory disorder in anoxic brain injury in greater detail. Hopkins et al. (1995b) found an intact recency effect for item recognition in the face of severe memory deficits in hypoxic patients, in common with amnesics of other etiologies. Hopkins et al. (1995c) also observed that anoxic participants' memory for temporal order and spatial location is better on tasks that utilize prior knowledge than on novel tasks.

The precise nature of the memory disturbance in anoxic patients most likely depends on which brain structures are affected and to what extent. Mackenzie Ross and Hodges (1997) found well preserved knowledge of famous people in the context of profound impairment of personally relevant autobiographical memory, which they suggested may be attributable to the multifocal neocortical damage sustained by this patient, who presented with generalized intellectual impairment and marked deficits in frontal executive function in addition to the memory deficit.

Personality change, drive, and executive function

Of the 67 individual cases under review, changes in personality and behavior or in some aspect of executive function were noted in 31 (46.2%). Although the memory deficit was often extensively examined, testing of other cognitive functions tended to be much less exhaustive (Maiese et al., 1988; Muramoto et al., 1979; Volpe & Hirst, 1983). Reporting on changes in behavior and personality was more often based on clinical observation of patients than on formal assess-

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ment. It was not surprising, therefore, often to find such reports in the psychiatric rather than in the neurological literature (Berlyne & Strachan, 1968; Collins & Jacobson, 1990; McNeill et al., 1965; Reich et al., 1983). Formal assessment of executive function tended to be limited to one or two tests, almost invariably with negative findings (Hopkins et al., 1995c) or with positive findings that were dismissed because they appeared to be anomalous (see, e.g., Hopkins et al., 1995a).

The most frequently reported change in personality was either emotional lability and impulsivity, or alternatively a lack of emotional expression. Both of these were often associated with lack of concern. The case of Brierley and Cooper (1962) was not only amnesic but was also said to have demonstrated emotional lability with violent temper tantrums that did not resolve. That of Parkin et al. (1987) was described as showing displays of despair which were often intense, uninhibited and prolonged. Ten of 20 individuals investigated by Bengtsson et al. (1969) were found to exhibit emotional shallowness, irritability, or a tendency to emotional lability.

Reich et al. (1983) reported on 6 survivors of cardiac arrest who suffered from only mild cerebral impairment, manifest primarily in personality changes and behavioral symptoms. The patients were distractible, irritable, and disinhibited, with disturbances of impulse control and loss of judgment. On mental status examination they showed bland or labile affect, rigid thought patterns, and major disturbances of insight, empathy, and self-awareness. In each case the symptoms were initially mistaken for depression.

A disorder of drive was cited in 13 of the 31 cases in this review considered to show disturbed behavior or personality changes. McNeill et al. (1965) reported the case of a 49-year-old woman who, following a cardiac arrest lacked drive and concentration, and demonstrated emotional lability in addition to being forgetful. Berlyne and Strachan (1968) characterized their patient as apathetic as well as amnesic, although they interpreted the inertia as a marker of a Korsakoff's psychosis rather than as a sign in its own right. Among the deficits noted in 2 of the 6 cases of Reich et al. (1983) were diminished drive and easy fatiguability, as well as flatness of affect.

In addition to other changes in personality, the case of Parkin et al. (1987) was described as showing no evidence of spontaneous conversation and an inability to initiate even the simplest act. Collins and Jacobson (1990) described a patient following attempted hanging with persisting problems which included a loss of initiative. Feve et al. (1993) examined movement and behavior in 4 cases whose primary deficit following anoxic brain injury was an axial motor impairment. Three of the 4 demonstrated inertia, with reduced language fluency also noted in 1. None of these patients was amnesic. All were shown to have bilateral lesions of the globus pallidus on MR scan.

Although such an important textbook as that by Lezak (1995) described a "reduced capacity for planning, initiating and carrying out activities" in association with anoxia, changes in executive function have attracted little attention in this etiology. Reduced executive function in this context refers to distractibility and difficulty with multiple tracking, impaired planning, and poor abstraction. Bengtsson et al. (1969) observed reduced attentiveness, difficulty with tasks requiring multiple tracking, new tasks or tasks requiring modification of behavior or response, as well as slowness of response in 10 of 20 patients. These authors either considered these symptoms to be negligible or to be attributable to some other cause of cerebral dysfunction. Reporting on 2 cases of "dementia" following episodes of anoxic ischemia, Volpe and Petito (1985) described, in addition to forgetfulness, inability to think abstractly, or to plan or complete actions.

Visuospatial deficits

Complex perceptual deficits are usually associated with lesions of the lateral occipitoparietal cortex bilaterally, an area that is thought to be particularly vulnerable in anoxic encephalopathy (Howard et al., 1987). Visuospatial or, less frequently, visual recognition problems were noted in 21 individual cases (31.3%) reviewed. Bengtsson et al. (1969) reported reduced spatial ability, though not visual agnosia, in 6 of 22 cases.

Parkin et al. (1987) reported difficulty in their patient's identification of pictorial representations of objects, animals or people especially when a figure–ground discrimination was required. She was also prosopagnosic. The case of Auerbach and Hodnett (1990) also displayed gross impairments in visual processing, involving a Balint's syndrome with disturbed visual scanning, poor eye–hand coordination and an inability to integrate visual input. Rizzo and Robin (1990) reported 2 cases who had simultanagnosia following cardiac arrest and who were shown to have bilateral infarctions in the superior visual association cortex of the occipital lobes on CT. An acquired dyslexia has also been described occasionally (Parkin et al., 1987; Willanger et al., 1970). Carbonnel et al. (1997) reported a case with visual associative agnosia without other kinds of perceptual deficit. The visuoperceptual problems reported in anoxic patients frequently occur in the context of widespread cognitive change (Auerbach & Hodnett, 1990; Parkin et al., 1987).

Language

Language has generally been considered to be preserved in anoxia (Roine et al., 1993; Volpe et al., 1986). Although language has not been examined extensively, in a number of studies it has been reported to be normal. For instance, Volpe et al. (1986) reported normal performance on the controlled word association test, preserved capacity to paraphrase proverbs and perfect performance on the Token Test in their participants. Zola-Morgan et al. (1986) tested case R.B. with Boston Naming and a screening aphasia battery and found no abnormalities other than an amnesic syndrome. Roine et al. (1993) tested word fluency, naming and

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comprehension of short sentences but there was no detail as to the tests used, while deficits were recorded only as the presence or absence of aphasia, identified as present in only 1 severely demented patient.

However, there have been more than occasional reports of disturbed language function in such patients, with expressive language problems more frequently reported than receptive difficulties. Meyer (1956) described persisting disorders of speech in 4 of 15 survivors of severe anoxia, including a reduction in spontaneous speech output, difficulty naming objects and a tendency to perseveration. In the papers under review, 6 patients (9%) were reported as having marked language impairment. Three of the patients considered by Bengtsson et al. (1969) to have evidence of cerebral impairment related to their cardiac arrest, either had word finding difficulties or impaired memory for names. In neither report was there any elaboration of the phenomenon. Amongst the 6 cases studied by Reich et al. (1983), 1, who had previously been a witty extemporaneous speaker, was noted to have word-finding difficulties and trouble completing sentences. Language was said to be the least affected function in the case of Parkin et al. (1987) but while comprehension was intact, she was described as having word finding difficulties resulting in often tortuous circumlocutions. The case of Carbonnel et al. (1997) was described as presenting a clinical picture involving a selective word comprehension deficit for animal names although abstract word comprehension was preserved.

Group Studies

Fourteen group studies involving 232 cases were reviewed. These included four abstracts (Armengol & Moes, 1986; Kotila & Kajaste, 1984; Maiese et al., 1988; Willanger et al., 1970). As indicated earlier, two of these investigations were directed at characterizing the memory deficit *per se* rather than outcomes of anoxic events, although other cognitive functions than memory were assessed (Hopkins et al., 1995b, 1995c). These two papers both report data for 11 cases, presumably the same, recruited from the same sources although that was not stated. The cases have only been counted once for this review.

Memory deficits were found to be a significant outcome in all 14 papers. In three of them an amnesic syndrome or a significant deterioration in recent memory function was considered to be the only significant outcome (Hopkins et al., 1995b; Maiese et al., 1988; Volpe et al., 1986).

In over half of these group studies, nine papers, changes in behavior, personality, or executive function were documented. Such changes were generally not well defined. Bigler and Alfano (1988) noted that additional, generalized cognitive impairment commonly accompanied the memory deficits. Earnest et al. (1980) found that the patient or family reported significant changes in the patient's personality or mental status in 12 of 20 cases still living 3 years after out-of-hospital cardiac arrest. Grosswasser et al. (1989) similarly reported undefined "behavioral disturbances" in 24 of 31 cases. In a study of 9 survivors of cardiac arrest, Yarnell (1976) noted that marked inability to retain new information was often accompanied by flat affect and loss of initiative. Wilson (1996) reported that the largest group in her series of 18 cases presented with deficits of both memory and executive functioning.

Kotila and Kajaste (1984) found that at follow-up all 10 patients in their study demonstrated lack of drive. Willanger et al. (1970) observed that in their cases with prolonged coma there was moderately severe intellectual impairment affecting both memory and "abstract functions," but the latter concept was not elaborated. Roine et al. (1993) claimed to have studied the "programming of activity," but this was done on the basis of observation and an unexplained rating system rather than by standardized examination. Nevertheless, they reported that 24 to 28% of their patients had problems with this aspect of cognition while 16 to 24% were said to have had problems with "motivation" at 12 months.

Six papers reported visuospatial deficits but again these were not well defined. All 10 cases in the study by Kotila and Kajaste (1984) were said to demonstrate constructional apraxia, while "spatial disturbances" were noted in 9. Armengol and Moes (1986) noted "impaired visuospatial functions" in all their 9 patients. Roine et al. (1993) reported visuoconstructive dyspraxia in 28% of cases 12 months following a cardiac arrest. Willanger et al. (1970) noted "spatial confusion" and visual agnosia in 1 case and "spatial confusion" and constructive apraxia in a second.

Most surprising, in view of the presumption that language is usually spared in this pathology, was that language was also found to be affected in 5 of these 13 studies. In a comparison of amnesic syndromes of different etiologies, Corkin et al. (1985) found that while all patients appeared to have normal language comprehension, and while there were no differences between the groups on a test of language comprehension (Token Test), the mean score for the anoxic patients was significantly lower than that for all other groups on a test (the Reporter's Test) used to assess language production. All of the 9 patients with anoxic encephalopathy studied by Armengol and Moes (1986) had linguistic problems to varying degrees. Grosswasser et al. (1989) reported that 29% of their cases were affected by memory disturbances as well as by a moderate-to-severe disability in communication reflected in their language, specifically in their naming ability. Kotila and Kajaste (1984) noted dysphasia in 4 of 10 patients in the acute phase following a cardiac arrest. They did not report specifically on the outcome in relation to language at follow-up 5 to 15 months later.

DISCUSSION

The most significant problem in comparing reports in this area is that the majority of studies of neuropsychological—as opposed to neurological—outcome have been retrospective. Only one group study, with sufficiently detailed neuropsychological assessment to be included in this review, was

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prospective (Roine et al., 1993). Most reported cases are therefore highly selected, with a view to demonstrating or describing a particular outcome or phenomenon associated with lesions in brain structures of interest. Cases with generalized, nonspecific, or focal deficits but not considered relevant to the particular hypothesis have tended to go unreported (Bhatia & Marsden, 1994).

Another issue was the enormous variability among studies in terms of the severity of anoxic events experienced by the participants and the period over which they were followed. For example, all patients in the study by Grosswasser et al. (1989) had a coma duration of more than 24 hr and all were referred for inpatient rehabilitation. In contrast, patients were only excluded from the study by Roine et al. (1993) if they responded to verbal commands immediately after resuscitation. The many sources of variability in the phenomenology of anoxic episodes themselves were reviewed in the introduction. Variability in selection of patients must add further to the heterogeneity of reported profiles of anoxic patients.

The Neuropathological Substrates of Cognitive Changes in Cerebral Anoxia

While most attention has focused on damage to the hippocampus following anoxic brain injury, damage to several brain regions has been demonstrated consistently. The basal ganglia, watershed cortex, thalamus, and cerebellum are all also liable to be affected. Furthermore, watershed cerebral cortex and the basal ganglia have been reported to be involved more frequently than the hippocampus, while the basal ganglia are more liable than the hippocampus to be the sole injured region. What is the relationship between the pattern of distribution of lesions and the documented neuropsychological sequelae of cerebral anoxia?

Neuropsychological Sequelae of Cerebral Anoxia

Memory

A disturbance of memory function was noted in 36 individual cases of 67 reviewed. In 13 cases the memory deficit was considered to be an isolated amnesic syndrome. Memory deficits were also found to be a significant outcome in 14 group studies, and the only significant outcome in 4 of these. These results confirmed that a memory deficit is a likely but not inevitable outcome of this pathology. They also suggested that most often the memory deficit occurs in the context of other cognitive change.

An association between amnesic disorders and the structures of the mesial temporal region, in particular the hippocampus, has long been established (Milner, 1966; Scoville & Milner, 1957; Shimauchi et al., 1989; Squire, 1992; Zola-Morgan & Squire, 1993). Circumscribed bilateral lesions of the CA1 field of the hippocampus have been identified in amnesic patients (Rempel-Clower et al., 1996; Zola-Morgan et al., 1986). At the same time it has been demonstrated that the hippocampus is one of the most vulnerable cerebral structures to anoxic conditions and, furthermore, that within the hippocampus the pyramidal neurones in the CA1 zone of the hippocampus are the most liable to compromise (Ng et al., 1989; Petito et al., 1987; Squire, 1992; Zola-Morgan et al., 1986). The amnesic syndrome that occurs in association with cerebral anoxia has therefore largely been attributed to hippocampal atrophy, with that pathology confirmed in a small number of cases (Cummings et al., 1984; Muramoto et al., 1979; Petito et al., 1987; Volpe & Hirst, 1983; Zola-Morgan et al., 1986, 1992).

However, the phenomenon of amnesia has not been associated exclusively with the hippocampus and postanoxic amnesia has not invariably been associated with hippocampal changes. Experimental evidence has demonstrated that lesions to the anterior thalamic nuclei, the fornix and the hippocampus can all produce comparable memory deficits (Aggleton & Sahgal, 1993; Gentilini et al., 1987; Graff-Radford et al., 1990; Mishkin, 1982; von Cramon et al., 1985). Neuropathological evidence has demonstrated an amnesic syndrome following hypotensive anesthesia, in the presence of only minor hippocampal lesions (Brierley & Cooper, 1962). In that case, significant cell loss was found both in the anterior nuclear complex and in the dorsomedial nucleus of the thalamus. This pattern of findings—with relative sparing of the hippocampus but marked lesions of the thalamus—was also confirmed in other cases (Adams et al., 1966) but without accompanying documentation of mental status.

It has also been suggested that there may be a characteristic memory deficit associated with lesions of the dorsolateral prefrontal cortex and caudate nucleus (Cummings, 1993). Unlike amnesic syndromes associated with lesions of the hippocampus or thalamus, frontal amnesic deficits are characterized by poor recall with relative preservation of recognition abilities. Cummings (1993) has argued that the reason for this is that the frontal–subcortical circuits mediate memory activation and search functions rather than storage; lesions produce deficits of information retrieval with relatively preserved recognition. Although the anoxic case of Cummings et al. (1984) did not show such a deficit, this outcome from cerebral anoxia has been identified (Volpe et al., 1986). No pathological correlation of such a finding has been demonstrated. The presence of a retrieval deficit in some but not all anoxic patients may be explained on the basis that some patients have a degree of disruption to the frontal system, by virtue of infarction of the frontal watershed cortex or because of basal ganglia involvement, or both.

Personality and behavior

Behavioral changes associated with lesions of the prefrontal region have been amply demonstrated (see, e.g., Fuster, 1989; Stuss & Benson, 1986). They include changes in such capacities as the orderly planning and sequencing of complex behaviors, the ability to attend to several components

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simultaneously or to alter flexibly the focus of concentration, the capacity to grasp the context and gist of a complex situation, the ability to follow multistep instructions, the inhibition of immediate but inappropriate response tendencies, and the ability to sustain behavioral output without perseveration (Mesulam, 1986).

Changes in personality, behavior or some aspect of executive function were noted in 31 individual cases of 67 reviewed and in 8 of 14 papers involving group studies. Such changes were frequently neither well defined nor vigorously investigated. Sometimes, changes in personality and behavior were observed but were dismissed as transient or inconsequential (Caronna, 1979; Finkelstein & Caronna, 1978; Volpe & Hirst, 1983). However, the alternative view—that these constitute some of the significant and permanent sequelae of cerebral anoxia—has also been strongly promoted. Indeed in a survey of amnesias of different etiologies, Signoret (1985) went so far as to suggest that because personality changes including indifference and apathy, as well as attentional difficulties are common in this setting, it is rare to find an isolated amnesic syndrome arising from anoxia.

Changes in personality and behavior in the studies under review were documented more often on the basis of observation than formal examination (Allison, 1956; Reich et al., 1983). Attempts to identify such phenomena through individual tests such as the Wisconsin Card Sorting Test or the FAS Verbal Fluency test generally failed (Hopkins et al., 1995b, 1995c; Volpe & Hirst, 1983). This lack of evidence of impairment on single tests has been interpreted as evidence of normal frontal function in anoxic patients. However it has been noted elsewhere that patients with frontal lesions may have quite unremarkable neurological and neuropsychological examinations and that quantifiable frontal system deficits in standard tests are not always impressive (Mesulam, 1986; Shallice & Burgess, 1991).

The anatomical specificity of "frontal lobe" syndromes (Cummings, 1993) has also been challenged by the observation of similar behavioral changes—including disorders of executive function, personality changes, and mood disturbances—in patients with lesions in other brain regions, most notably the basal ganglia (Alexander & Crutcher, 1990; Bhatia & Marsden, 1994; Richfield et al., 1987; Strub, 1989). The most commonly reported changes associated with basal ganglia lesions include loss of motivation and initiative, loss of cognitive flexibility, reduction in both mental and behavioral activities, blunting of affect, and reduced or altered verbal output (Damasio et al., 1982; Galynker et al., 1995; Laplane et al., 1984; Naeser et al., 1982; Richfield et al., 1987; Strub, 1989). This phenomenon has been explained on the basis of the connectivity between separate regions of the basal ganglia each of which projects to a different part of the frontal lobes (Alexander et al., 1986; Alexander & Crutcher, 1990; Bhatia & Marsden, 1994; Cummings, 1993; Mendez et al., 1989).

Although behavioral syndromes have been observed in the presence of lesions to both frontal cortex and the basal ganglia, there has been scant documentation of the neuropathological underpinnings of such behavioral changes in the context of anoxic events. However, there has been suggestive functional imaging. In the study of Strub (1989) although MRI showed no evidence of damage to the frontal cortex itself a decrease in blood flow in the right superior frontal lobe was demonstrated by single photon emission computed tomography (SPECT). In positron emission tomography (PET) studies of 7 patients all with behavioral changes associated with lesions presumed to be restricted to the lentiform nuclei, Laplane et al. (1989) found significant cortical glucose hypometabolism in lateral and mediofrontal cortical regions in most participants in the absence of cortical atrophy. The latter authors specifically raised the question as to whether the observed frontal hypometabolism might be a remote effect of the lentiform lesions due to deafferentation of frontal cortex.

On the basis of these studies, and given the neuropathological outcomes identified in cerebral anoxia it is possible to speculate that in cerebral anoxia anterior brain regions may be liable to insult from dual mechanisms: both by virtue of a direct effect on vascular supply of oxygen to the cortex itself and by virtue of a disconnection of the anterior cortex from the basal ganglia.

Visuospatial deficits

Visual agnosia and associated visuoperceptual problems have been identified in the context of bilateral damage to the occipital visual radiations, the parietal lobes, or to the inferior temporo–occipital junction. Sufficient pathology for the production of visual object agnosia includes either extensive left medial occipital lobe destruction or bilateral cortical–subcortical occipital lobe lesions with disconnection of visual areas from both the left speech area and the limbic system (Bauer & Rubens, 1985). The rarity of these syndromes is likely to be due first to the fact that if the optic radiations are damaged by infarcts of greater size visual field defects rather than agnosias are produced; and second, if of smaller size then precise bilateral lesions are required (Alexander & Albert, 1985). Although there were some dramatic cases with bizarre and profound perceptual deficits amongst the cases reviewed, complex perceptual deficits or visual recognition deficits were observed in only 21 individual cases.

In cerebral anoxia, the watershed cortex including posterior watershed areas has been frequently found to be compromised. In most reported cases this has resulted in less profound perceptual disturbances than either a visual object agnosia or a Balint's syndrome. Such deficits were found in 5 of 13 group studies but were typically not well defined. Severe perceptual problems were identified in only a small number of single-case studies (Auerbach & Hodnett, 1990; Parkin et al., 1987). Where the perceptual disturbance has been closely examined, the perceptual problem itself has formed the focus of the study in question with the anoxic etiology merely incidental (see, e.g., Milner et al., 1991; Rizzo & Robin, 1990).

Language

Although language function is generally regarded as being spared in this pathology, there is considerable evidence that expressive language may be impaired. The most striking evidence for this proposition in the studies reviewed here was that defective language was identified as a significant outcome in 5 of the 14 group studies. In every case expressive rather receptive language function was identified as problematic. The study by Corkin et al. (1985) was the only one specifically to address this question; they found that while amnesics of different etiologies did not differ in the performance on a test of language comprehension, anoxic patients scored substantially worse on a test of language production. A neuropathological basis for a language disorder in anoxia has never been addressed. However, descriptions of transcortical motor aphasia arising principally from damage to the anterior watershed zones bear a striking resemblance to the expressive language disorder described in anoxic patients: preserved comprehension and repetition accompanied by impaired naming (Benson, 1993).

There is a rich and informative literature on the subject of behavioral and cognitive outcomes from cerebral anoxia that has been largely ignored in the pursuit of a specific phenomenon, that of a relatively isolated amnesic syndrome in the context of damage to the hippocampus. Such a pure outcome only infrequently results from anoxic events. Analysis of neuropathological and structural imaging studies of patients with cerebral anoxia clearly demonstrates that a network of brain regions is liable to be compromised. This network involves the watershed cortex, the basal ganglia and the thalamus, as well as the hippocampus. Detailed review of published cases reveals that the watershed cortex, the basal ganglia and the thalamus are all just as likely as the hippocampus, if not more so, to be compromised by an anoxic event.

Although in recent studies the most attention has been paid to an amnesic syndrome following anoxic episodes, the clinical presentation of anoxic patients is as likely to manifest as changes in personality, behavior and executive function as it is in an amnesic syndrome. Disorders of visuoperceptual function and of expressive language have also been identified repeatedly. This constellation of deficits has been shown to fit very well with identified neuropathological outcomes from anoxic events.

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Appendix

AUTHORS AND CASES INCLUDED IN THIS REVIEW

Neuropathological Studies

Adams et al. (1966)	11 cases
Brierley & Cooper (1962)	1 case
Cummings (1984)	1 case
Ginsberg et al. (1976)	3 cases
Meyer (1956)	6 cases
Petito et al. (1987)	14 cases
Rempel-Clower et al. (1996)	3 cases
Revesz & Geddes (1988)	1 case
Volpe & Petito (1985)	2 cases
Zola-Morgan et al. (1986)	1 case

Structural Imaging Studies

Boylan et al. (1990)	1 case
Hopkins et al. (1995b)	11 cases
Hori et al. (1991)	1 case
Kjos et al. (1983)	10 cases
Murray et al. (1987)	5 cases
Ohkawa & Yamadori (1993)	1 case
Press et al. (1989)	1 case
Roine et al. (1993)	52 cases
Sawada et al. (1990)	1 case
Takahashi et al. (1993)	6 cases
Tippin et al. (1984)	1 case

Individual Case Studies

Allison (1956)	10 cases
Auerbach & Hodnett (1990)	1 case
Bengtsson et al. (1969)	20 cases
Berlyne & Strachan (1968)	1 case
Brierley & Cooper (1962)	1 case
Carbonnel et al. (1997)	1 case
Collins & Jacobson (1990)	1 case
Cummings et al. (1984)	1 case
Feve et al. (1993)	4 cases
Hopkins et al. (1995)	3 cases
Mackenzie Ross & Hodges (1997)	1 case
McNeill et al. (1965)	1 case
Medalia et al. (1991),	2 cases
Milner et al. (1991)	1 case
Muramoto et al. (1979)	1 case
Parkin et al. (1987)	1 case
Reich et al. (1983)	6 cases
Rempel-Clower et al. (1996)	3 cases
Rizzo & Robin (1990)	2 cases
Volpe & Hirst (1983)	3 cases
Volpe & Petito (1985)	2 cases
Whiteley (1958)	1 case

Group Studies

Armengol & Moes (1986)	9 cases
Bigler & Alfano (1988)	12 cases
Corkin et al. (1985)	3 cases
Earnest et al. (1980)	20 cases
Finkelstein & Caronna (1978)	10 cases
Grosswasser et al. (1989)	31 cases
Hopkins et al. (1995a, 1995b)	11 cases
Kotila & Kajaste (1984)	10 cases
Maiese et al. (1988)	9 cases
Roine et al. (1993)	59 cases
Volpe et al. (1986)	6 cases
Willanger et al. (1970)	25 cases
Wilson (1996)	18 cases
Yarnell (1976)	9 cases

Historical Studies

Fletcher (1945)
Meyer (1956)
Steegman (1951)

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