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Neuroimaging Studies in Carbon Monoxide Intoxication

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1. Introduction

CO is a tasteless, odorless and colorless gas. The existence of endogenous CO in the human body arises from heme catabolism (Meredith and Vale 1988; Ernst and Zibrak 1998) and oxidation of organic molecules (Marilena 1997). Endogenous CO acts as a neurotransmitter for long-term potentiation, consequently playing a key role in memory and learning (Marilena 1997). It also plays a role in modulating inflammation, apoptosis, cell proliferation, mitochondrial biogenesis (Weaver 2009) and vascular relaxation (Marilena 1997).

Exogenous sources of CO intoxication include smoking, forest fires, pollutants, and improper usage of heaters or furnaces (Weaver 2009; Kumar, Prakash et al. 2010). CO intoxication usually indicates exposure to exogenous sources and is considered one of the most common causes of poisoning worldwide (Prockop and Chichkova 2007; Weaver 2009), with 1000 deaths annually in Britain (Meredith and Vale 1988), and 4000-6000 deaths annually in the United States (Tibbles and Perrotta 1994; Ernst and Zibrak 1998; Weaver 1999). In Asia, the exact epidemiology remains unclear. In Japan, Hong Kong and Taiwan, a common CO etiology of intoxication is charcoal burning suicide (Lee, Chan et al. 2002). In Japan, poisoning by charcoal burning is the most lethal form of suicide and is a highly prevalent method among men aged 25-64 years of age (Kamizato, Yoshitome et al. 2009), in contrast to a high rate of drug poisoning as a method of suicide in women. In Hong Kong, the risk factors of suicide by charcoal burning are male and living alone with financial stress (Lee and Leung 2009). In Taiwan, charcoal burning was not a common method of suicide before 1998, with a rate of only 0.14 per 10⁵ people per year (Lin and Lu 2008). With the dissemination of media and the internet, the rate of charcoal burning suicides dramatically increased by 40-fold, reaching a rate of 5.38 per 10⁵ people per year in 2005 (Lin and Lu 2008).

2. Mechanisms of CO intoxication

2.1 Tissue hypoxia

CO competes with oxygen in binding with hemoglobin to form carboxyhemoglobin. The affinity between CO and hemoglobin is 200 times higher than that of oxygen (Ernst and Zibrak 1998; Piantadosi 2002; Weaver 2009). The production of carboxyhemoglobin shifts the oxygen-hemoglobin curve to the left and dissociates oxygen from hemoglobin (Ernst and Zibrak 1998). These reactions consequently reduce oxygen delivery to tissues and result in a hypoxic microenvironment.

2.2 Oxidative stress

In brief, CO intoxication leads to oxidative stress through the following mechanisms:

1. CO increases cytosolic heme levels leading to increased heme oxygenase-1 protein, causing intracellular oxidative stress and direct cellular injury (Ernst and Zibrak 1998; Weaver 2009).
2. CO binds to cytochrome c oxidase and impairs mitochondrial function. Cytochrome c oxidase is one of the mitochondrial complexes involved in electric chain transport and is essential for energy production. Binding of CO to cytochrome c oxidase can lead to activation of hypoxia-inducible factor 1 α or production of reactive oxygen species with direct cellular injury. Related downstream reactions include apoptosis, lipid peroxidation, lymphocyte proliferation, inflammation and necrosis (Weaver 2009).
3. CO binds to platelet heme protein and induces biogenesis of nitric oxide peroxynitrite, consequently leading to enhanced adhesion of neutrophils to the vascular lining, neutrophil aggregation and release of myeloperoxidase. All of these reactions not only trigger inflammatory processes but also produce more reactive oxygen species (Ernst and Zibrak 1998; Weaver 2009).

2.3 Reoxygenation injury

H₂O₂ production has been noted to increase extensively in brain tissues during reoxygenation after CO intoxication (Zhang and Piantadosi 1992). Salicylate hydroxylation products and 2,3- and 2,5-dihydroxybenzoic acid are also significantly increased during reoxygenation. During this period, CO still binds to cytochrome c oxidase and inhibits the mitochondrial electron transport chain. If the reaction exists in iron-rich regions such as the basal ganglia, it causes persistent acidosis and active iron, which can further damage cells (Zhang and Piantadosi 1992).

2.4 Mechanisms related to central nervous system (CNS) injury

2.4.1 Acute CNS injury

In animal models, an initial cerebral blood flow increment after CO exposure is thought to maintain the baseline energy state (MacMillan 1975). A change of blood flow depends on both the reaction of the cerebrovasculature and cardiac function in CO intoxication. In either failure of cerebrovasculature dilatation or impairment of cardiac pumping function, there is no compensatory blood supply increase in the status of acute carboxyhemoglobin elevation and oxyhemoglobin reduction. (Raub and Benignus 2002). After initially compensated hyperperfusion, focal hypoperfusion has been noted in several studies (Choi, Lee et al. 1992; Choi and Lee 1993) which might be related to clinical manifestation (Sesay, Bidabe et al. 1996). Hypoperfusion over the basal ganglion (Sesay, Bidabe et al. 1996; Kao, Hung et al.

1998), cerebral cortical (Choi, Lee et al. 1992; Kao, Hung et al. 1998), and white matter (WM) (Sesay, Bidabe et al. 1996) areas have been noticed. Cerebral WM and the globus pallidum (GPi) were noted to have relatively low cerebral blood flow after acute CO intoxication in one animal study (Okeda, Matsuo et al. 1987).

Hypoxia in the CNS induces decreased adenosine-5'-triphosphate, influx of Ca^{2+} and Na^{+} , release of glutamate, noradrenaline and acetylcholine and causes cell swelling and death (Weinachter, Blavet et al. 1990; Kluge 1991). Increased glutamate with both neuronal necrosis and apoptosis was noted immediately after CO intoxication in one animal study (Piantadosi, Zhang et al. 1997). However, how hypoxia affects the CNS in the acute stage of CO intoxication has not been well established (Piantadosi, Zhang et al. 1997; Gorman, Drewry et al. 2003). Aside from changes of cerebral blood flow and hypoxia, increasing intracranial pressure and brain tissue necrosis have been noted in animals and humans after acute CO intoxication (Jiang and Tyssebotn 1997; Piantadosi, Zhang et al. 1997; Uemura, Harada et al. 2001; Lo, Chen et al. 2007).

2.4.2 Chronic CNS injury

The pathogenesis of delayed CNS injury in CO intoxication is complicated. Hypoperfusion (Sesay, Bidabe et al. 1996; Watanabe, Nohara et al. 2002; Chu, Jung et al. 2004) and hypoxia (Opeskin and Drummer 1994) still play an important role. Demyelination (Murata, Kimura et al. 2001; Kamijo, Soma et al. 2007; Ide and Kamijo 2008), cytotoxic edema (Kim, Chang et al. 2003; Chu, Jung et al. 2004; Kwon, Chung et al. 2004), hemorrhage (Ramsey 2001) and infarction (Schwartz, Hennerici et al. 1985; Sung, Yu et al. 2010) have also been associated with delayed neurological deficits. Hypoperfusion and cytotoxic edema in delayed CNS injury have been noted in WM areas and the cerebral cortex (Chu, Jung et al. 2004), and ischemia and necrosis have been noted in the globus pallidus (Chang, Han et al. 1992). Although demyelination and axonal damage might co-exist in CO intoxication, demyelination more than axonal damage is suggested in the literature (Chang, Han et al. 1992; Murata, Kimura et al. 2001; Kamijo, Soma et al. 2007; Ide and Kamijo 2008).

2.5 Other mechanisms

CO also inhibits a number of proteins essential for cells. Myoglobin in the heart and skeletal muscle systems, neuroglobin in the brain, cytochrome P450 (Weiner 1986), dopamine and tryptophan oxygenase (Raub and Benignus 2002) have all been reported to be affected. A high CO concentration transforms xanthine dehydrogenase to xanthine oxidase and produces more free radicals in tissues (Piantadosi, Tatro et al. 1995). Inhibiting the normal function of these intracellular proteins causes further damage or systemic injury in CO intoxication.

3. Clinical manifestation

3.1 The diagnosis of CO intoxication

The diagnosis of CO intoxication is based on the clinical history of exposure or elevated carboxyhemoglobin level ($> 10\%$) (Handa and Tai 2005; Chang, Lee et al. 2009). There is currently no definition of clinical staging in CO intoxication in the literature, although the pathophysiology follows that of hypoxic-ischemic encephalopathy (Gutierrez, Rovira et al.).

3.2 Symptoms in the acute phase

Tightness across the forehead, headache, throbbing in the temples, nausea, vomiting, dimness of vision, dizziness, general weakness, syncope, convulsion, and coma are commonly found in patients with CO exposure within one day (Choi 2001). Cortical blindness with initially normal visual evoked potentials has also been reported in a case (Katafuchi, Nishimi et al. 1985). The pathogenesis contributing to the clinical manifestations includes change of blood flow (Penney 1990; Lo, Chen et al. 2007), hypoxia (Lo, Chen et al. 2007), and neurochemistry abnormalities (Penney 1990).

3.3 Symptoms in the late phase

Following initial neurological deficits after acute CO intoxication, some patients experience progressive neurological deterioration, while others nearly complete recovery of symptoms. Some patients have a delayed onset of neurological deficits after an initial symptom-free period (Lee and Marsden 1994). The latter is often termed as delayed neuropsychiatric sequela in CO intoxication. The lucid interval after acute CO poisoning, on average, is around 20 days, varying from one to 240 days (Choi 1983; Lee and Marsden 1994; Ernst and Zibrak 1998; Pavese, Napolitano et al. 1999; Hsiao, Kuo et al. 2004), with a prevalence of 0.2-40% (Hsiao, Kuo et al. 2004; Otubo, Shirakawa et al. 2007). Delayed neuropsychiatric sequelae include parkinsonism (Lee and Marsden 1994), chorea (Park and Choi 2004), akinetic mutism (Lee and Marsden 1994), increased irritability, verbal aggressiveness, violence, impulsiveness (Meredith and Vale 1988), mood disorders (Weaver 2009), dementia (Meredith and Vale 1988; Ernst and Zibrak 1998; Weaver 2009), psychosis (Ernst and Zibrak 1998), sleep disturbances (Weaver 2009), cortical blindness (Quattrocchio, Leotta et al. 1987; Senol, Yildiz et al. 2009) and incontinence (Ernst and Zibrak 1998).

The cognitive deficits are often very diverse (Hurley, Hopkins et al. 2001; Parkinson, Hopkins et al. 2002; Raub and Benignus 2002) including impairment in verbal or visual episodic memory, language, visuospatial ability, executive function and calculation (Chang, Chang et al. 2010). No specific neuropsychiatric battery has been designed for the cognitive deficits in CO intoxication. For general cognitive performance, most researchers apply the mini-mental state examination (Folstein, Folstein et al. 1975) or Wechsler Adult Intelligence Scale (Dorken and Greenbloom 1953) for evaluation. Chang *et al.* (Chang, Lee et al. 2009) used the clinical dementia rating scale (Morris 1997) to evaluate the functional capability of these patients since they may have physical disabilities. Tasks that have been used for evaluation are as follows: Alzheimer's Disease Assessment Scale-Cognitive word-recognition test (Rosen, Mohs et al. 1984) for verbal episodic memory; recollection of Rey-Osterrieth complex figures for visuospatial ability (Boone 2000); Boston naming test for language ability (Boone 2000); digit span, digit-symbol, digit backward (Cronholm and Viding 1956; Sherman and Blatt 1968; Rudel and Denckla 1974); Trail Making Part A and Part B, block design, and design fluency (Giesecking, Lubin et al. 1956; Arbuthnott and Frank 2000) for executive function; and neuropsychiatric inventory for behavioral changes (Cummings, Mega et al. 1994).

4. Neuroimaging study results of CO intoxication by anatomical classification

4.1 Basal ganglion lesions emphasized on the globus pallidus (GP)

The basal ganglion includes the putamen, caudate nucleus, and GP. GP lesions are often considered as pathognomonic signs for patients with CO intoxication, however the

prevalence differs among studies (Silver, Cross et al. 1996; O'Donnell, Buxton et al. 2000). One study showed 63% of abnormal lesions in the GP with 26% in the rest of the basal ganglia (O'Donnell, Buxton et al. 2000). Another study with 73 patients revealed only one patient (1.4%) with basal ganglia lesions scanned two weeks after CO poisoning (Parkinson, Hopkins et al. 2002).

4.1.1 Imaging features suggesting edematous change in the acute phase

Low density GP lesions, commonly seen in computed tomography (CT), are considered as characteristic findings in patients with CO intoxication (Kanaya, Imaizumi et al. 1992; Gotoh, Kuyama et al. 1993; Uchino, Hasuo et al. 1994; Chu, Jung et al. 2004; Kinoshita, Sugihara et al. 2005; Hopkins, Fearing et al. 2006). Low density lesions of the putamen and caudate nucleus, in contrast, have only been reported in one case (Ferrier, Wallace et al. 1994). The nature of GP lesions has been studied further by diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping (Chu, Jung et al. 2004; Kinoshita, Sugihara et al. 2005). One case report interpreted low ADC values and high intensity GP lesions on DWI as restriction of water diffusion (i.e. cytotoxic edema) (Kinoshita, Sugihara et al. 2005). Vasogenic edema can also be visualized on ADC and DWI as increased signal intensity lesions (Chalela, Wolf et al. 2001). The high signal on DWI is due to the T2 shine-through effect.

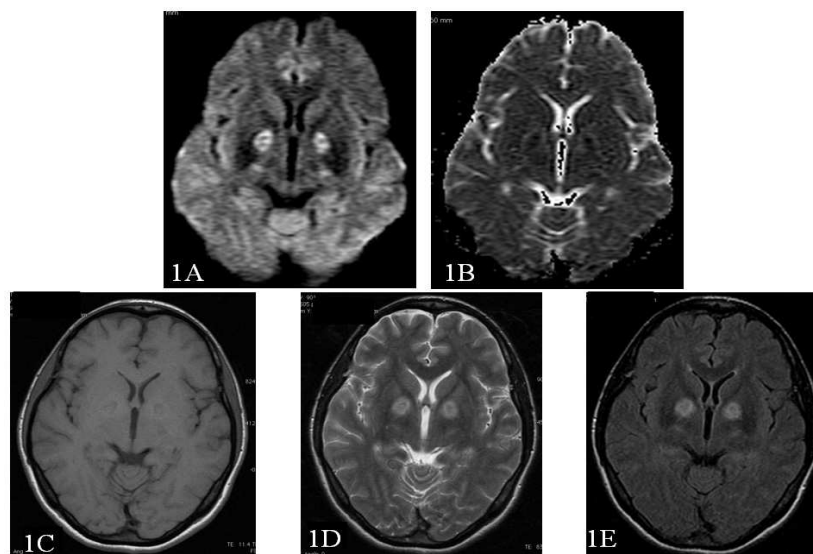


Fig. 1. Magnetic resonance imaging study in the acute stage of carbon monoxide intoxication.

Six days after CO intoxication, a 42-year-old woman with a globus pallidus interna lesion with hyperintensity in diffusion weighted imaging (1A), hypointensity in apparent diffusion coefficient (1B), hypointensity in T1 weighted image (WI) (1C), hyperintensity in T2WI (1D), and hyperintensity in fluid-attenuated inversion recovery (1E).

4.1.2 Imaging features suggesting necrosis

Imaging studies showing cavity-changes by T1 or T2WI often suggest necrosis of the GP (Mendelsohn and Hertzanu 1983; Pulst, Walshe et al. 1983; Ko, Ahn et al. 2004). Autopsies of patients with CO intoxication have confirmed the histology of necrosis and/or neuronal degeneration of the GP (Jones, Lagasse et al. 1994). The pathogenesis of necrosis is believed to be due to edema-induced ischemia or hemorrhage transformation (Chang, Han et al.

1992). Follow-up GP images often show volume shrinkage (Vieregge, Klostermann et al. 1989; Kanaya, Imaizumi et al. 1992).

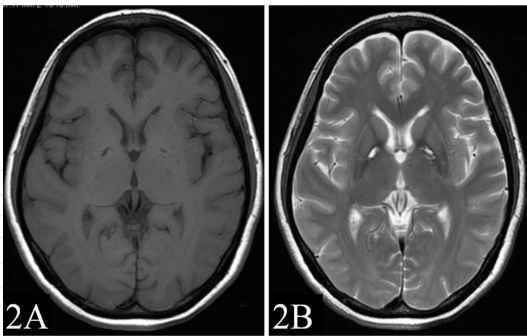


Fig. 2. Magnetic resonance imaging in the delayed stage of carbon monoxide intoxication.

Four years after CO intoxication, a 41-year-old woman with a globus pallidus lesion showed hypointensity in T1 weighted image (T1WI) (2A) and cavity changes with hyperintensity in T2WI (2B).

4.1.3 Imaging features suggesting hemorrhage

Hemorrhage of the GP is seen both in the acute and delayed stages after CO intoxication (Silverman, Brenner et al. 1993; Bianco and Floris 1996), while only one case report has demonstrated putaminal hemorrhage by CT (Schils, Cabay et al. 1999). Temporal sequences in conventional MRI have been noted to be similar to intracranial hemorrhage (Bradley 1993). Hemorrhage may occur within days after CO intoxication with high signal intensity in T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI) (Bianco and Floris 1996). High T1WI and low T2WI signals have been observed up to two months after intoxication, suggesting delayed hemorrhage (Yoshii, Kozuma et al. 1998). One case report described abnormal signals in the GP, with shorter T1 characteristics and longer T2 characteristics suggesting a prior focal hemorrhage three years after CO intoxication (Silverman, Brenner et al. 1993). In one study, widespread multiple pin point hemorrhages in the thalamus and GP were found in 40% of postpartum autopsies (Mehta, Niyogi et al. 2001).

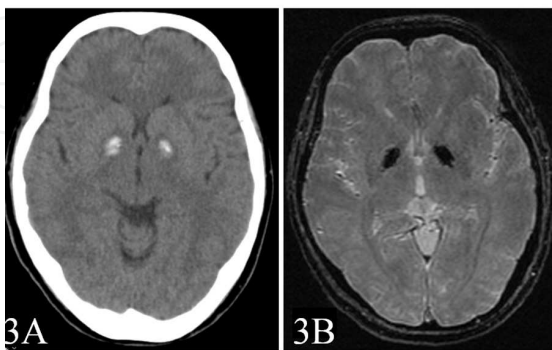


Fig. 3. Computed tomography and gradient echo T2WI after carbon monoxide intoxication.

Two days after CO intoxication, a 57-year-old woman with hemorrhage in the globus pallidus showed hyperdensity in CT (3A) and a follow-up one month later with low signal intensity on gradient echo (3B).

4.1.4 Imaging features suggesting calcification

Calcification of the GP has also been reported in the literature (Illum 1980; Lugaresi, Montagna et al. 1990; Adam, Baulac et al. 2008). The clinical presentations included acute neurological deficits with loss of initiative and slowness of thinking and acting (Adam, Baulac et al. 2008), and delayed neurological deficits with personality changes and akinesia (Lugaresi, Montagna et al. 1990). However one case was free of any neurological sequelae after 48 years of follow-up (Illum 1980).

4.1.5 Functional imaging features suggesting hypometabolism

[^{18}F]fluorodeoxyglucose (FDG) PET has been used to evaluate glucose metabolism activity. Decreased metabolism in the basal ganglion and frontal lobe has been frequently reported (Tengvar, Johansson et al. 2004; Hon, Yeung et al. 2006). The largest series on PET and CO intoxication with basal ganglion lesions included eight patients with their behavioral and MRI patterns (Laplane, Levasseur et al. 1989). Seven patients revealed hypometabolism of the prefrontal cortex in relation to other parts of the brain, leading to a concept of prefrontal-pallidum circuit dysfunction. A functional study using [^{18}F] F-DOPA showed presynaptic dopaminergic deficits in one case with parkinsonism symptoms after CO intoxication (Rissanen, Paavilainen et al. 2010). In this case, normal uptake of [^{11}C] raclopride implicated normal postsynaptic dopaminergic function (Rissanen, Paavilainen et al. 2010).

Single photon emission computed tomography (SPECT) provides perfusion patterns of GM and the basal ganglion (Chang, Liu et al. 2008) with tracers such as $^{99\text{m}}\text{Tc}$ -ethylcysteinate dimer and $^{99\text{m}}\text{Tc}$ -Hexamethylpropyleneamine oxime. ($^{99\text{m}}\text{Tc}$ -ECD) brain SPECT is considered to be more sensitive than brain CT for the early detection of hypoperfusion status (Wu, Changlai et al. 2003). In the acute stage, 50% to 85% of the patients with CO intoxication have been reported to have basal ganglion hypoperfusion (Wu, Changlai et al. 2003; Pach, Hubalewska et al. 2004).

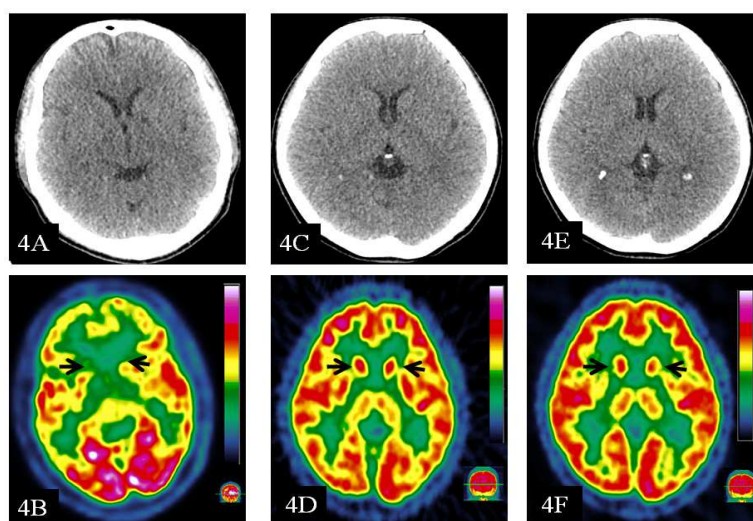


Fig. 4. [^{18}F]fluorodeoxyglucose positron emission tomography (PET) of two patients after CO poisoning.

Two and a half months after CO intoxication, a 33-year-old patient's CT showed low intensity of the globus pallidus (4A) on brain computed tomography (CT) while PET revealed a remarkably reduced uptake of FDG in bilateral striatum (arrows) and thalamus (4B). Five months after CO intoxication, another 36-year-old patient's CT showed no

obvious lesions (4C, 4E) while PET revealed normal FDG uptake in bilateral striatum (4D, 4F arrows) and normal thalamic uptake.

4.1.6 Imaging features suggesting pallidoreticular damage

In CO intoxication, pallidoreticular damage specifically targeting the fiber tract along the pallidum and substantia nigra pars reticulata was first described by Auer and Benveniste (Auer and Benveniste 1996). One case report revealed cytotoxic edema of bilateral GP with concurrent substantia nigra pars reticulata involvement in a patient scanned 12 days after CO intoxication (Kinoshita, Sugihara et al. 2005). Two case reports revealed pallidoreticular distribution after one year showing hyperintensities on T2WI and hypointensities on T1WI (Kawanami, Kato et al. 1998; Gandini, Prockop et al. 2002). The authors suggested that these two iron rich regions had selective tissue vulnerability due to the high affinity of CO to heme molecules (Kawanami, Kato et al. 1998; Gandini, Prockop et al. 2002; Kinoshita, Sugihara et al. 2005).

4.2 WM lesions

An increasing number of studies have established that WM lesions are the most common findings in CO intoxication patients, either in the acute phase or in those with delayed neuropsychiatric sequelae (Miura, Mitomo et al. 1985; Chang, Han et al. 1992; Choi, Kim et al. 1993; Lee and Marsden 1994). The largest study included 129 patients, and 33% of them had WM lesions on brain CT (Choi, Kim et al. 1993). In patients with improvements of neurological deficits, resolution of WM changes have also been noted (Klostermann, Vieregge et al. 1993; Matsushita, Takahashi et al. 1996; Pavese, Napolitano et al. 1999). Lesions of the WM area are believed to be associated with clinical outcomes (Miura, Mitomo et al. 1985; Vieregge, Klostermann et al. 1989; Choi, Kim et al. 1993).

4.2.1 Imaging features suggesting WM cytotoxic/vasogenic edema

In a pathological series, cytotoxic and vasogenic edema after CO intoxication were often mixed within three months, and the presence of cytotoxic edema was often noted to be in the acute phase (Ginsberg, Myers et al. 1974; Ginsberg 1985; Thom, Bhopale et al. 2004). The presence of cytotoxic edema lesions can be detected as early as the first day of CO intoxication (Sener 2003) or during the delayed phase (Murata, Kimura et al. 2001; Kim, Chang et al. 2003; Chu, Jung et al. 2004). Imaging features suggesting cytotoxic edema of the

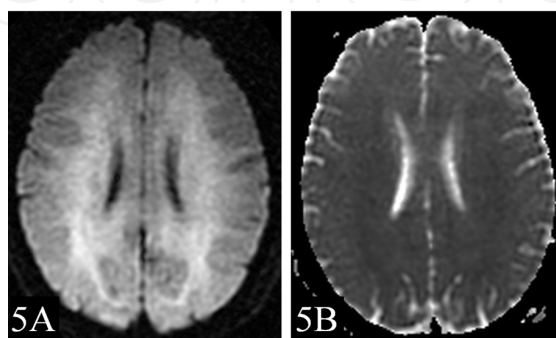


Fig. 5. Diffusion weighted image (5A) and apparent diffusion coefficient (5B) in one case presenting as delayed neuropsychiatric sequelae after carbon monoxide intoxication.

WM area show low ADC values with high DWI intensities, while vasogenic edema shows high signals on both sequences.

One month after CO intoxication, a 41-year-old woman with white matter hyperintensity in DWI (6A) and iso- to low-signal intensity in ADC (6B) indicating cytotoxic edema.

4.2.2 Imaging features suggesting WM demyelination or axonopathy

The prevalence of imaging features suggesting WM demyelination or axonopathy range from 12% to 100% in CO intoxication (Chang, Han et al. 1992; Parkinson, Hopkins et al. 2002). The largest MRI study focusing on WM included 73 patients scanned on day 1, 2 weeks and 6 months after CO intoxication (Parkinson, Hopkins et al. 2002). Semiquantitative scores were rated on bilateral periventricular and centrum semiovale areas (Parkinson, Hopkins et al. 2002). Twelve percent of the patients had WM hyperintensities on T2WI on day 1 (Parkinson, Hopkins et al. 2002) with significantly more periventricular, but not centrum semiovale distributions as compared with age-matched controls. The WM lesions in the CO group did not change from day 1 to 6 months follow-up, however the hyperintensities in the centrum semiovale were related to worse cognitive performance. The study revealed no correlation between WM hyperintensities and carboxyhemoglobin level, or duration of CO exposure at any of the three scan times (Parkinson, Hopkins et al. 2002).

Hyperintensities in T2WI and fluid-attenuated inversion recovery (FLAIR) and hypointensities in T1WI often suggest WM demyelination or axonopathy (Chang, Han et al. 1992; Pavese, Napolitano et al. 1999; Parkinson, Hopkins et al. 2002). From a pathological perspective, myelin damage is constant and can vary from discrete perivascular lesions to extensive periventricular demyelination and/or axonal destruction (Funata, Okeda et al. 1982; Prockop and Chichkova 2007). An autopsy study after CO intoxication showed that diffuse WM hyperintensities reflected apoptosis of oligodendrocytes (Akaiwa, Hozumi et al. 2002). Another autopsy study of brains three days after CO intoxication revealed a normal cortex and injured WM with disrupted myelin and pyknotic oligodendroglia, whilst the axons, astrocytes and capillaries were normal (Foncin and Le Beau 1978).

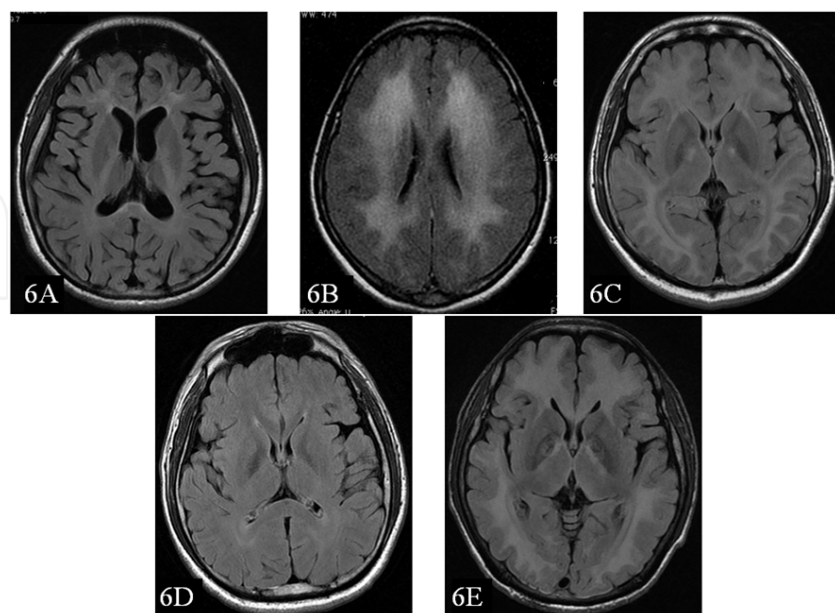


Fig. 6. A wide spectrum of white matter hyperintensities in fluid-attenuated inversion recovery after carbon monoxide intoxication with cognitive deficits.

Focal white matter hyperintensities (WMHs) over bilateral frontal horns in a 29-year-old woman, two years after CO exposure (6A). Diffuse and confluent WMHs in a 42-year-old woman, one and a half months after CO exposure (6B). Prominent subcortical U fiber hyperintensity with globus pallidus hyperintensity in a 35-year-old man, one and a half months after CO exposure (6C). A 31-year-old woman presented in a confused state without obvious WMHs four days after CO intoxication (6D). Extensive subcortical WMHs with globus pallidus hypointensity two years later (6E).

A study by Weaver (Weaver, Valentine et al. 2007) suggested that cognitive sequelae at six weeks benefited from hyperbaric oxygen (HBO) in patients aged 36 years and older, or who were exposed to CO for a duration of 24 hours or more. Two studies explored changes of fractional anisotropy (FA) in CO intoxication after HBO. Both studies revealed lower FA values in the patient group compared to that of controls three months after HBO (Lo, Chen et al. 2007; Chang, Lee et al. 2009). The mini-mental state examination scores completely recovered after three months of follow-up in all evaluated patients in one study (Lo, Chen et al. 2007), while another study showed that HBO treatment may not reverse the damage caused by CO intoxication (Chang, Lee et al. 2009). A longitudinal study used diffusion tensor imaging (DTI) and compared the changes of diffusion measurements in CO intoxication patients including mean diffusivity, axial diffusivity and radial diffusivity with follow-up scans three months and 10 months later. Extensive changes found in the FA maps at both three and 10 months in the CO group were attributed to initial increments of radial diffusivities, while a decrement of axial diffusivities were found at 10 months follow-up (Chang, Chang et al. 2010). The study suggested that changes in diffusion parameters might reflect WM demyelination at three months followed by subsequent axonopathy.

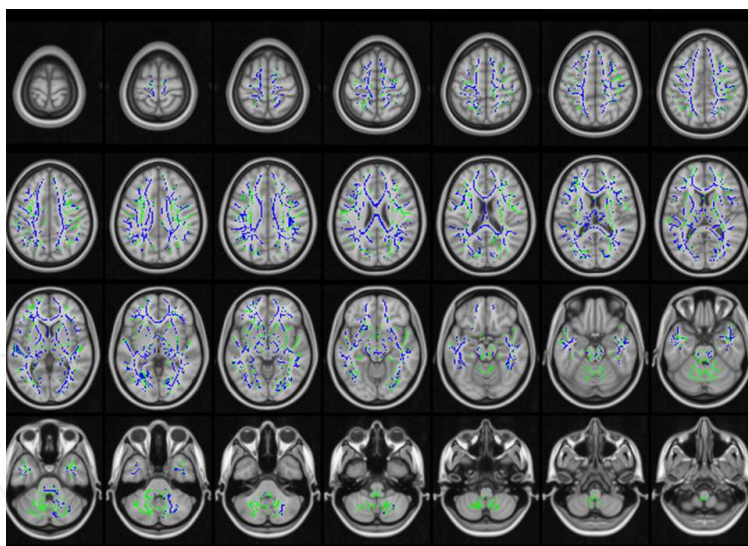


Fig. 7. An example of Tract Based Spatial Statistics with decreased Fractional Anisotropy (FA) (blue) overlaid on the mean FA skeleton (green) in a sample of carbon monoxide intoxication (n=30) as compared with age-matched controls. Diffuse white matter damage was detected including the subcortical areas, brain stem and cerebellum.

White matter insults after CO intoxication lead to transient or permanent injuries, which consequently lead to decreased WM volumes. Diffusion indices including mean diffusivity, axial diffusivity and radial diffusivity reflect WM injuries earlier than volume reduction, while the major regions of WM atrophy in one study were in the periventricular WM areas (Chang, Chang et al. 2010).

4.2.3 Imaging features suggesting WM hemorrhage

In the acute phase, petechial hemorrhages of the WM, particularly the corpus callosum, are common (Funata, Okeda et al. 1982; Finelli and DiMario 2004; Weaver and Hopkins 2005). Gradient echo T2WI uses a shorter repetition time than spin-echo T2WI and can detect metal material such as ferritin and ferritin-containing substances such as hemosiderin, thus detecting hemorrhages and microbleeds (Atlas, Grossman et al. 1988; Bradley 1993). Susceptibility-weighted imaging (SWI) is a heavy T2*-weighted gradient-recalled 3-D fast low-angle shot sequence with full flow compensation in all three directions (Sehgal, Delproposto et al. 2005). Microhemorrhages have been reported in patients with CO intoxication with the complimentary information provided by gradient echo T2WI and SWI (Finelli and DiMario 2004; Weaver and Hopkins 2005). In gradient echo T2WI, hemorrhages along the nerve fibers are distributed predominantly over the posterior WM (Finelli and DiMario 2004).

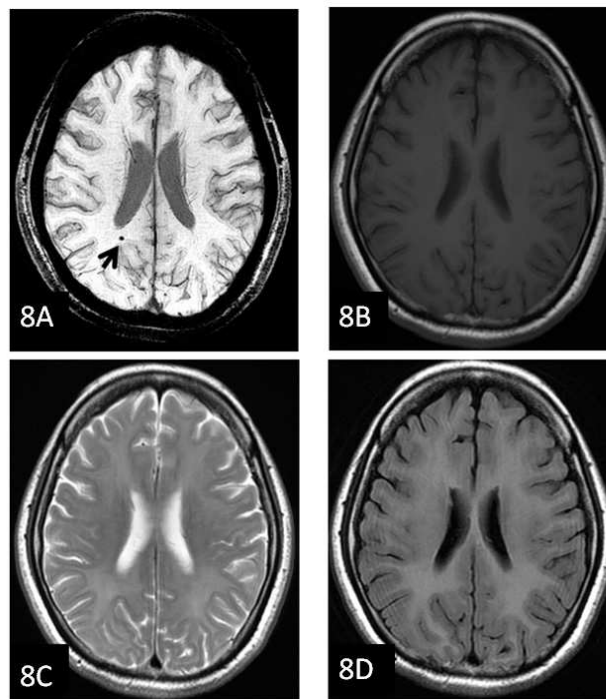


Fig. 8. Microhemorrhage shown on susceptibility-weighted imaging.

Four months after carbon monoxide intoxication, a 53-year-old woman with a low signal intensity lesion on susceptibility-weighted imaging (8A, arrow) suggesting microhemorrhage of white matter which was invisible on T1 (8B), T2 (8C), and fluid-attenuated inversion recovery (8D).

4.3 Cortex

4.3.1 Imaging features suggesting cortical injury and atrophy

Pure cortical involvement without concurrent WM lesions in CO intoxication is not common (Choi, Kim et al. 1993). Using DWI, imaging features suggesting cortical cytotoxic edema were described in bilateral posterior temporal lobes and bilateral occipital lobes in one patient, bilateral posterior temporal lobes and left parietal lobe in

another patient, and right frontal, temporal and parietal lobes in another (Hon, Yeung et al. 2006). Hippocampal involvement has been linked with anterograde amnesia, with pathological findings of necrosis and apoptosis (Uemura, Harada et al. 2001; Mahmoud, Mestour et al. 2009).

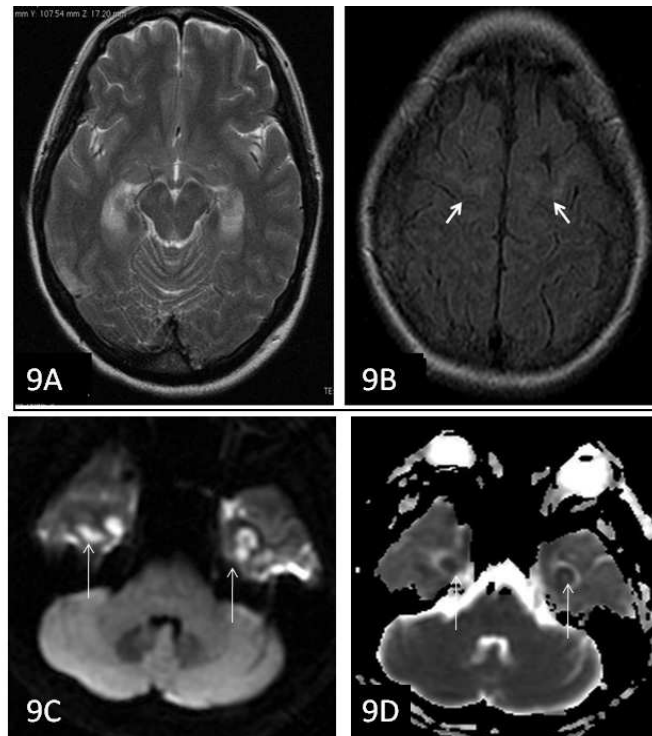


Fig. 9. Cortical injuries after CO intoxication.

Four days after CO intoxication, a 37-year-old woman with hyperintensities in bilateral hippocampi in a T2-weighted image (9A). Six days after CO intoxication, a 42-year-old woman with hyperintensities in bilateral superior frontal gyrus in fluid-attenuated inversion recovery (9B). Another 28-year-old female five days after CO intoxication showed bilateral medial temporal region high signal intensity lesions (9C, diffusion weighted image, arrows) with corresponding low intensity lesions on apparent diffusion coefficient map (9D, arrows) suggesting cytotoxic edema.

Cortical volume reduction is a late consequence of CO intoxication. Significant ventricle and sulcus dilatation in comparison with the controls were found in all 34 patients evaluated during the chronic phase of CO intoxication in a study by Kono et al. (Kono, Kono et al. 1983), with a 19-year interval from CO intoxication. In a case report several months after CO intoxication, brain MRI revealed bilateral atrophy of lateral temporal lobes and the clinical deficits included severe cognitive impairment and a transient Klüver-Bucy-like behavior (Muller and Gruber 2001). Voxel based morphometry (Ashburner and Friston 2001) enables the quantification of grey and WM volume changes between groups. In one study using voxel based morphometry, no significant differences in the GM were found in the patient group compared to age-matched controls ten months after CO intoxication (Chang, Chang et al. 2010), while atrophy of WM was evident in the periventricular areas. In another study of 13 patients with brain MRI studies 25 years after CO poisoning, the parieto-occipital region was most frequently involved, and six of the 13 patients had dilated temporal horns (Uchino, Hasuo et al. 1994).

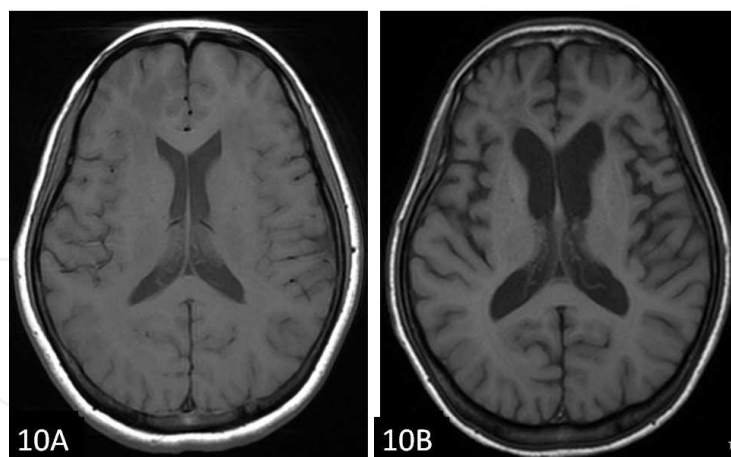


Fig. 10. Cortical atrophy after carbon monoxide intoxication revealed in T1-weighted image.

A 47-year-old woman with rapid cortical atrophy after CO intoxication as revealed in T1WI three months (9A) and 20 months (9B) after CO exposure.

4.3.2 Imaging features suggesting cortical hemorrhage

Hemorrhage in the cortical areas has also been reported in CO intoxication. One 28-year-old man had achromatopsia five months after CO intoxication (Fine and Parker 1996). Brain MRI revealed hemorrhage in the bilateral temporal and occipital lobes (Fine and Parker 1996). Another case demonstrated a 7-year-old boy who had generalized convulsions, coma and right hemiparesis on the day of CO intoxication (El Khashab and Nejat 2009). Brain CT on the same day revealed a left temporal hemorrhage (El Khashab and Nejat 2009). Microvascular impairment and brain reperfusion injury were the suspected pathogenetic mechanisms causing the damage (El Khashab and Nejat 2009).

4.3.3 Imaging features suggesting cortical hypoperfusion and hypometabolism

Six studies have reported SPECT findings in the evaluation of cortical blood flow after CO intoxication (Choi, Lee et al. 1992; Choi, Kim et al. 1995; Watanabe, Nohara et al. 2002; Pach, Hubalewska et al. 2004; Huang SH, Chang Chiung Chih2 et al. 2005; Pach, Urbanik et al. 2005). The largest one included 20 cases with 85% of the patients showing hypoperfusion over the frontal-parietal cortex (Pach, Hubalewska et al. 2004). In a study on follow-up SPECT in patients with CO intoxication, six of seven patients had improvement of hypoperfusion throughout the cortex, while their clinical conditions also improved concomitantly (Choi, Kim et al. 1995). In a comparison between those with delayed neuropsychiatric sequelae and those without sequelae, significant hypoperfusion was noted over bilateral frontal lobes, bilateral insula and right temporal lobe in patients with delayed neuropsychiatric sequelae, whilst only bilateral frontal lobe hypoperfusion was noted in those without neuropsychiatric sequelae (Watanabe, Nohara et al. 2002).

To date, there have only been a limited number of reports on [^{18}F] FDG-PET in the evaluation of metabolic dysfunction in the cortical areas of patients with CO intoxication (Tengvar, Johansson et al. 2004; Senol, Yildiz et al. 2009). One case report of a middle-aged man revealed hypometabolism of bilateral frontal lobes and anterior cingulate cortices (Tengvar, Johansson et al. 2004), and his neurological deficit of akinetic mutism was regarded as the consequence of

the hypometabolism state of the involved regions (Tengvar, Johansson et al. 2004). In a study of serial [^{18}F] FDG-PET follow-up scans, persistent hypometabolism of bilateral frontal lobes was found in a 29-year-old woman who demonstrated impaired responsiveness to stimuli for one year after CO poisoning (Shimosegawa, Hatazawa et al. 1992). In another case report on a 21-year-old woman who had coma, seizure and cortical blindness within three days after CO poisoning, the neurological deficit of cortical blindness remained. A subsequent [^{18}F] FDG-PET four years later still showed hypometabolism of bilateral posterior temporal and occipital lobes (Senol, Yildiz et al. 2009).

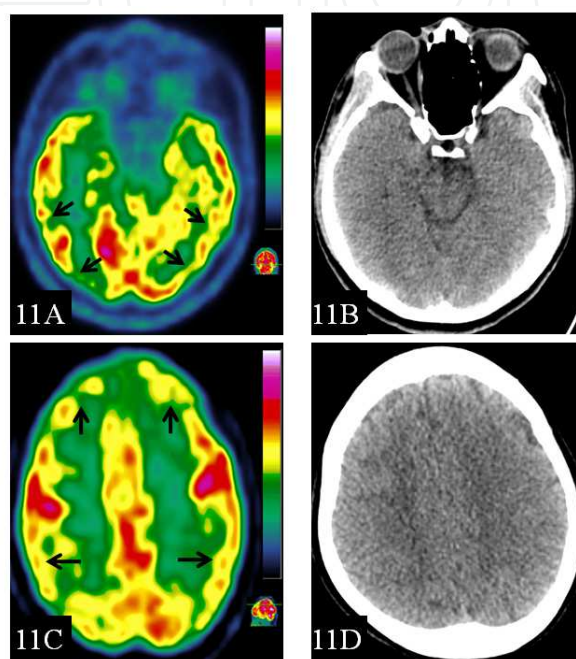


Fig. 11. [^{18}F]fluorodeoxyglucose positron emission tomography of two patients after carbon monoxide intoxication.

One month after CO intoxication, a patient's (age: 30) PET revealed reduced uptake of FDG in bilateral temporal and occipital lobes (11A, arrows), while the brain CT (11B) did not detect any hypodense lesions over the corresponding areas. One month after CO intoxication, another patient's (age: 58) PET revealed reduced uptake of FDG in bilateral frontal and parietal lobes (11C, arrows) with negative findings on the CT scan (11D).

5. Nerves and muscles

Although peripheral neuropathy has been reported in CO intoxication (Choi 1982), only electrophysiological studies but not neuroimaging studies are available (Choi 1982).

Skeletal muscle injuries have been reported in CO intoxication. In one case report, skeletal muscle MRI was performed showing hyperintensity lesions in T2WI of the thigh muscles three months after CO intoxication (Chen, Huang et al. 2010). The muscle biopsy in this patient proved the diagnosis of heterotopic ossification selectively involving the iliopsoas, the tensor fascia lata, rectus femoris, sartorius and quadriceps muscles. Another study using Tc99m-sestamibi SPECT to evaluate the skeletal muscular injuries in 25 patients after CO intoxication showed decreased uptake in the patient group as compared with the controls (Huang, Chang et al. 2011). The low uptake was related to mitochondrial dysfunction.

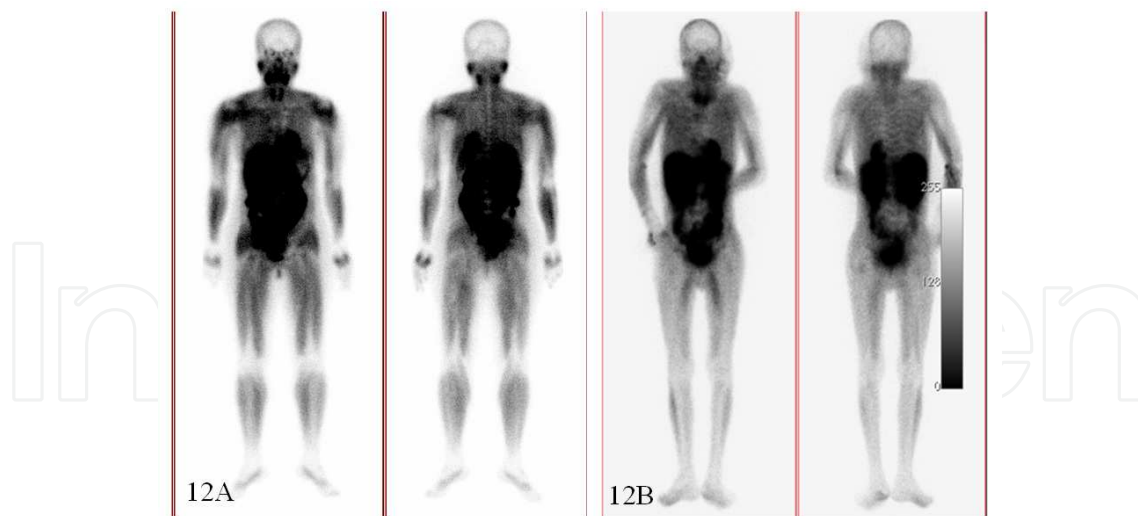


Fig. 12. Planar view of technetium-99m-sestamibi (^{99m}Tc -MIBI) in the evaluation of muscle injury in a patient with carbon monoxide intoxication.

Compared with muscle ^{99m}Tc -MIBI of a normal control (12A), a 59-year-old man showed decreased ^{99m}Tc -MIBI uptake in the thigh muscles two months after CO intoxication (12B).

6. Conclusion

Damage to the neurological system after CO intoxication includes the basal ganglia, cerebral WM, cortex and muscles. The mechanisms of damage can be identified by MRI and correlated with clinical features. Apart from MRI, functional imaging can provide information about brain perfusion and metabolism in CO intoxication. With muscle MIBI, mitochondrial function can be assessed in patients with CO intoxication.

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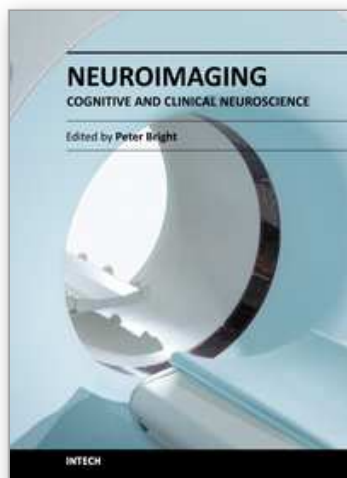
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The rate of technological progress is encouraging increasingly sophisticated lines of enquiry in cognitive neuroscience and shows no sign of slowing down in the foreseeable future. Nevertheless, it is unlikely that even the strongest advocates of the cognitive neuroscience approach would maintain that advances in cognitive theory have kept in step with methods-based developments. There are several candidate reasons for the failure of neuroimaging studies to convincingly resolve many of the most important theoretical debates in the literature. For example, a significant proportion of published functional magnetic resonance imaging (fMRI) studies are not well grounded in cognitive theory, and this represents a step away from the traditional approach in experimental psychology of methodically and systematically building on (or chipping away at) existing theoretical models using tried and tested methods. Unless the experimental study design is set up within a clearly defined theoretical framework, any inferences that are drawn are unlikely to be accepted as anything other than speculative. A second, more fundamental issue is whether neuroimaging data alone can address how cognitive functions operate (far more interesting to the cognitive scientist than establishing the neuroanatomical coordinates of a given function - the where question).

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