

# Cerebral reserve capacity: implications for alcohol and drug abuse

George Fein\*, Victoria Di Sclafani

*Neurobehavioral Research Inc., 201 Tamal Vista Boulevard, Corte Madera, CA 94925, USA*

Received 12 September 2003; received in revised form 16 October 2003; accepted 18 October 2003

## Abstract

Cerebral reserve capacity (or functional reserve) refers to the brain's ability to maintain function when confronted by degenerative processes. Functional reserve can be estimated by several associated measures, including premorbid brain size, premorbid IQ, and level of education attained. There is accumulating evidence that the magnitude of reserve capacity is important in determining the onset and progression of the clinical manifestations of neurodegenerative brain diseases. Normal aging also whittles away at this cerebral reserve, and there may be a consequent unmasking of morbid effects that was not clinically evident when this compensatory reserve was sufficient. We review the evidence supporting this model for a number of degenerative brain processes, including Alzheimer's disease, presenile dementia, HIV dementia, aging, and chronic (multiyear) substance abuse. The concept of cerebral functional reserve has important implications for alcohol and drug abuse morbidity. First, given the high genetic contribution to substance abuse, there is an increased likelihood that the parents of substance abusers were substance abusers themselves. Substance abuse during pregnancy can inhibit brain growth, resulting in reduced brain size and reduced reserve capacity (and therefore less ability to compensate for loss of function later in life). Second, substance abuse is often coupled with poverty, and both substance abuse and poverty are associated with some of the same conditions that reduce brain growth. Finally, we comment on the most important public health implication of the cerebral reserve capacity model (*vis-à-vis* addiction). © 2004 Elsevier Inc. All rights reserved.

*Keywords:* Functional reserve; Reserve capacity; Brain size; Alcoholism; Addiction; Aging; Dementia; Alzheimer's disease

## 1. The brain functional reserve model

The model of a cerebral functional reserve (or reserve capacity) that influences the time of onset and the clinical progression of neurodegenerative diseases has solidified over the past two decades. Reserve capacity refers to the concept that the larger premorbid brain has a greater number of neurons and synapses (assuming the same neuronal and synaptic density among individuals) (Haug, 1987). This "extra" capacity acts as a functional reserve, ameliorating cognitive decline in the face of neurologic insult or disease. This simple model, wherein larger premorbid brains are associated with greater brain reserve capacity, does not hold across the entire human population, but, rather, holds within populations in which brain structure and function are relatively homogeneous. For example, it does not hold across sexes. There have been a number of studies whose results have revealed fundamental sex differences in the structure of the human cerebral cortex that may underlie specific abilities and susceptibilities to diseases affecting the neocortex (Rabinowicz et al., 1999, 2002; Reiss et al., 1996). These differ-

ences may also affect reserve capacity and its ability to ameliorate the effects of disease. The brain reserve capacity model is likely to hold within relatively homogeneous populations in which individuals reach different brain sizes because of genetic factors, and the achievement of full brain growth can be retarded by untoward influences, such as disease, trauma, or malnutrition.

The functional reserve hypothesis was first introduced by Katzman et al. (1988) in a postmortem investigation of Alzheimer's disease. They studied 137 nursing home residents and found 10 individuals whose autopsy revealed a quantity of neocortical plaques comparable to that observed in patients with Alzheimer's disease, but whose cognitive performance was comparable to that of control subjects (non-demented subjects without Alzheimer's disease or other brain lesions). In addition, the brain weights and number of large neurons in these cognitively normal patients with high quantity of plaque were significantly greater than those of the control group. Katzman et al. concluded that these clinically healthy individuals with high quantity of plaque had incipient Alzheimer's disease, but were cognitively intact because of a greater neuronal reserve associated with their larger than average brains.

Mori et al. (1997), in a magnetic resonance imaging (MRI) study of 60 patients with probable Alzheimer's disease, found that many of the cognitive abilities tested were

\* Corresponding author. Tel.: +1-415-927-6888; fax: +1-415-924-2903.

E-mail address: george@nbresearch.com (G. Fein).

Editor: T.R. Jerrells

significantly and positively correlated with premorbid brain volume, and that these associations were independent of the effects of age, sex, and education level. Mori et al. concluded that premorbid brain volume was a determinant of reserve capacity, and they postulated a threshold concept (i.e., that dementia emerges after the exhaustion of this reserve). Graves et al. (1996), in a population-based study of 1,985 Japanese-Americans aged 65 years and older who resided in King County in Washington state, examined the relation between head circumference (i.e., premorbid brain size, because skull growth is driven by brain growth) and scores on the Cognitive Abilities Screening Instrument. Among people with Alzheimer's disease (after controlling for age, sex, and education level), there was a strong negative association between head circumference and the severity of cognitive impairment. They observed that persons with both Alzheimer's disease and a small premorbid brain suffered either an earlier onset or a more rapid clinical progression of the disease than those with a larger premorbid brain.

Schofield et al. (1995) showed that the age of onset of Alzheimer's disease was correlated with premorbid brain size in a computerized tomography study of 28 female patients with probable Alzheimer's disease. They hypothesized that cognitive abilities stayed within the greater reserve capacity associated with larger brains for a longer period, thereby delaying the onset of dementia. Bigio et al. (2002) examined synaptic loss in presenile versus senile-onset Alzheimer's disease. They found that synaptic loss (i.e., lower synaptophysin levels) was greater, neuritic plaque counts were higher, more neurofibrillary tangles were present, and brain weight was lower in younger versus older individuals with Alzheimer's disease. Assuming that normal aging causes a loss of synapses, there are more synapses in the brains of persons in their fifth and sixth decades than in the brains of persons in their seventh and eighth decades. "Assuming next that some unknown 'threshold' of synapses must be reached before cognitive impairment occurs, then more synapses must be lost at earlier ages to reach that threshold and produce disorders such as AD [Alzheimer's disease]" (Bigio et al., 2002, p. 225).

Cabeza et al. (2002) examined the role of functional reserve in high-performing older adults. Noting that some older adults show significant cognitive deficits whereas others perform as well as young adults, they investigated the neural bases of these different patterns of age-related cognitive performance using positron emission tomography. Their study was designed to test two opposing models of prefrontal cortex activity, which tends to be less asymmetric in older than in younger adults [see reviews by Cabeza and Nyberg (2000) and Fletcher and Henson (2001)]. The less asymmetric use of prefrontal cortex in older adults may help counteract age-related neurocognitive decline (the compensation model) by recruiting additional brain regions to help with performance. In the dedifferentiation model, it may reflect an age-related difficulty in recruiting specialized neural mechanisms. Cabeza et al. compared the compensation

model to the dedifferentiation model by measuring prefrontal cortex activity in younger adults, low-performing older adults, and high-performing older adults. They assessed subjects during an easy and a more difficult memory task: recall memory (the simplest of memory tasks) and source memory (i.e., individuals must remember whether they heard or saw a stimulus). Source memory, compared with recall memory, was more highly associated with right prefrontal cortex activations in younger adults. During the source memory task, low-performing older adults recruited similar right prefrontal cortex regions as the younger adults, but high-performing older adults engaged the prefrontal cortex regions bilaterally. These findings support the suggestion that low-performing older adults recruit a similar network as recruited by young adults, but they use it inefficiently. In contrast, high-performing older adults counteract age-related neural decline through the use of functional reserve (and plastic reorganization of neurocognitive networks). These results are consistent with the compensation hypothesis and inconsistent with the dedifferentiation hypothesis.

Larger reserve capacity may improve the prognosis of neurodegenerative processes. Ernst et al. (2002) studied cognitively normal individuals seropositive for HIV versus cognitively normal individuals seronegative for HIV using functional MRI to look at a working memory task. The sample seropositive for HIV showed a greater magnitude of brain activation in the lateral prefrontal cortex than observed for the sample seronegative for HIV. This greater use was not present in other areas activated during the task. The sample seropositive for HIV also performed comparably to the sample seronegative for HIV on a battery of neuropsychologic tests. Ernst et al. suggested that the delayed appearance of the clinical manifestations of early injury to the prefrontal cortex neural substrate in the patients who were seropositive for HIV was due to recruitment of prefrontal reserve capacity.

According to brain reserve theory, level of education attained is a likely derivative of functional reserve (i.e., individuals are more likely to attain a high level of education if their reserve capacity is high). Consistent with this statement, results of incidence studies of dementia have shown that low education level increases the risk of Alzheimer's disease and other types of dementia (Cobb et al., 1995; Glatt et al., 1996; Katzman, 1993). Low education level also increases the incidence of memory loss and other cognitive decline short of dementia (Blum & Jarvik, 1974; Colsher & Wallace, 1991; Evans et al., 1993; Plassman et al., 1995; Scherr et al., 1988; Schmand et al., 1997; Snowdon et al., 1996). Satz (1993), in a review of functional reserve theory, suggests that intelligence is a more valid indirect measure of cerebral reserve than is education level. He argues that education attainment is co-determined by factors other than an individual's capacity to learn (e.g., socioeconomic circumstances), whereas intelligence more directly reflects cerebral reserve. Schmand et al. (1997) directly tested Satz's hypothesis by studying individuals in the Amsterdam Study

of the Elderly, a population-based sample of 2,063 individuals aged 65 through 84 years. They examined the association of the incidence of dementia with both education level and intelligence estimates (from the Dutch Adult Reading Test). They found that low estimated IQ scores predicted dementia incidence better than education did, consistent with the predictions of functional reserve theory.

Many investigators have documented the persistent cognitive deficits found as a result of chronic (multiyear) alcohol or crack cocaine dependence [reviewed in Di Sclafani et al. (2002) and Fein et al. (1990)]. We and colleagues in our laboratory evaluated the relation of cognitive performance (using a battery of neuropsychologic tests) and premorbid brain size (using MRI to find the volume of the intracranial vault, which is an indirect measure of premorbid brain size) in individuals dependent on crack cocaine only ( $n = 19$ ) or on crack cocaine and alcohol ( $n = 28$ ) (Di Sclafani et al., 1998). The intracranial vault volume accounted for 14.1% ( $P = .009$ ) of the variance of the global clinical impairment score (a composite variable reflecting clinical cognitive impairment) in the combined substance-dependent sample (crack only-dependent and crack and alcohol-dependent). The intracranial vault volume also explained a significant proportion of the variance in all cognitive domains (attention, abstraction, spatial abilities, memory, learning, and reaction time). These effects became even larger after the variance associated with peak cocaine dose (the only drug or alcohol use variable associated with the severity of neuropsychologic impairments) was removed.

In summary, there is overwhelming evidence that the human brain uses its functional reserve to compensate for cerebral morbidity associated with diseases and aging. Clinical impairment arises as degenerative processes overwhelm this reserve capacity. This model is supported by results of small studies of clinical samples, population studies, and studies of exemplary cognitive performance in the elderly.

## 2. Factors affecting functional reserve capacity

Differences among individuals in brain size, which strongly affect reserve capacity, may entirely reflect normal variability among individuals. However, reduced brain size may also reflect the effects of a poor prenatal or early childhood environment on brain development. Individuals subjected to developmental insults (e.g., a significantly pre-term birth) or deprived of developmental aids to brain growth (e.g., a stimulating early childhood environment and adequate nutrition) are likely to develop smaller brains (Cole & Cole, 1993; Stoch et al., 1982). The consequent reduced reserve capacity is likely to exacerbate later cerebral morbidity (e.g., from the effects of substance abuse or even normal aging).

Findings from many studies show that maternal addiction to cocaine, alcohol, or heroin during pregnancy has a long-term, deleterious effect on head (and therefore brain) size

(Chasnoff et al., 1986; Day et al., 1994; Feng, 1993). A dose-response effect of maternal cocaine use on newborn head circumference has been documented (Bateman & Chiriboga, 2000). Heavy prenatal alcohol exposure reduces region-specific brain growth through adolescence (Sowell et al., 1996). Even severe maternal psychosocial stress may reduce the head circumference of the newborn (Lou et al., 1994).

The consequences of reduced brain size at birth can follow an individual throughout his or her life. Pre-term, very low birth weight children show persistent ill effects in cognitive and school performance (Hack et al., 1996; Hack & Taylor, 2000). Even among full-term births, children born small for gestational age (i.e., within the lowest 3% of gestational length and weight) have school difficulties when tested at both 12 and 18 years of age (Larroque et al., 2001).

## 3. Public health implications

Developmental environments detrimental to brain growth are likely to exacerbate cognitive impairment because of later substance abuse. This association is part of a nexus of risk for the poor, because deficient prenatal care and early childhood malnutrition and psychosocial deprivation are often related to poverty. In the United States, female-headed households are the hardest hit. The poverty rates for these single mothers and their children (under 6 years of age) are 60.5% for Whites, 71.8% for Hispanics, and 73.1% for African-Americans (DiNitto, 1995). Moreover, poverty and substance abuse often affect the same inner-city populations. Not only are impoverished children less likely to possess adequate brain reserves to compensate for the effects of drug and alcohol abuse, they also struggle in an unstable and disadvantaged social structure. For example, given the high genetic contribution to substance abuse, there is a high likelihood that many drug and alcohol abusers have substance-dependent parents. This increases the probability of poor nutrition and (maternal) drug and alcohol abuse during pregnancy, as well as for a less than thriving environment for the young child. The worst-case scenario is that these children, who already have inadequate cerebral reserves owing to a detrimental developmental environment, may complete the generational cycle by becoming substance dependent themselves.

Finally, the functional reserve model has important implications for the prognosis of the older alcohol- or drug-dependent individual. Aging may unmask cognitive impairments caused by earlier substance abuse in individuals who completely recovered function with the attainment of abstinence by middle age. In multigenerational alcohol- or drug-dependent individuals, this now apparent cognitive impairment compounds the effects of their reduced reserve capacity. In such individuals, the dramatic "third strike" could be cerebrovascular disease (an increased risk in substance abusers), Alzheimer's disease, or even (simply) the declining cognitive abilities associated with normal aging.

The public health implications of the brain reserve capacity model for alcoholism and drug abuse are dramatic. They cry out that the morbidity of alcoholism or drug addiction cannot be viewed without considering the context in which it occurs. When alcoholism or drug addiction occurs in poverty or in multigenerational substance-abusing families, the morbidity is exacerbated. Public policy, treatment, and social services must take the issues raised above into account to be realistic and effective in addressing the problem of alcohol and drug abuse morbidity.

### Acknowledgments

This work was supported by grants AA11311 (G.F.) and AA13659 (G.F.), from the National Institute on Alcohol Abuse and Alcoholism, and grant DA09453 (G.F.), from the National Institute on Drug Abuse.

### References

- Bateman, D. A., & Chiriboga, C. A. (2000). Dose-response effect of cocaine on newborn head circumference. *Pediatrics* 106, E33 (Abstract).
- Bigio, E. H., Hynan, L. S., Sontag, E., Satumtira, S., & White, C. L. (2002). Synapse loss is greater in presenile than senile onset Alzheimer disease: implications for the cognitive reserve hypothesis. *Neuropathol Appl Neurobiol* 28, 218–227.
- Blum, J. E., & Jarvik, L. F. (1974). Intellectual performance of octogenarians as a function of education and initial ability. *Hum Dev* 17, 364–375.
- Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage* 17, 1394–1402.
- Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: an empirical review of 275 PET and fMRI studies. *J Cogn Neurosci* 12, 1–47.
- Chasnoff, I. J., Burns, K. A., Burns, W. J., & Schnoll, S. H. (1986). Prenatal drug exposure: effects on neonatal and infant growth and development. *Neurobehav Toxicol Teratol* 8, 357–362.
- Cobb, J. L., Wolf, P. A., Au, R., White, R., & D'Agostino, R. B. (1995). The effect of education on the incidence of dementia and Alzheimer's disease in the Framingham Study. *Neurology* 45, 1707–1712.
- Cole, M., & Cole, S. (1993). *The Development of Children*. New York: Scientific American.
- Colsher, P. L., & Wallace, R. B. (1991). Longitudinal application of cognitive function measures in a defined population of community-dwelling elders. *Ann Epidemiol* 1, 215–230.
- Day, N. L., Richardson, G. A., Geva, D., & Robles, N. (1994). Alcohol, marijuana, and tobacco: effects of prenatal exposure on offspring growth and morphology at age six. *Alcohol Clin Exp Res* 18, 786–794.
- DiNitto (1995). *Social Welfare: Politics and Public Policy*. Needham Heights, MA: Allyn & Bacon.
- Di Sclafani, V., Clark, H. W., Tolou-Shams, M., Bloomer, C. W., Salas, G. A., Norman, D., & Fein, G. (1998). Premorbid brain size is a determinant of functional reserve in abstinent crack-cocaine and crack-cocaine-alcohol-dependent adults. *J Int Neuropsychol Soc* 4, 559–565.
- Di Sclafani, V., Tolou-Shams, M., Price, L. J., & Fein, G. (2002). Neuropsychological performance of individuals dependent on crack-cocaine, or crack-cocaine and alcohol, at 6 weeks and 6 months of abstinence. *Drug Alcohol Depend* 66, 161–171.
- Ernst, T., Chang, L., Jovicich, J., Ames, N., & Arnold, S. (2002). Abnormal brain activation on functional MRI in cognitively asymptomatic HIV patients. *Neurology* 59, 1343–1349.
- Evans, D. A., Beckett, L. A., Albert, M. S., Hebert, L. E., Scherr, P. A., Funkenstein, H. H., & Taylor, J. O. (1993). Level of education and change in cognitive function in a community population of older persons. *Ann Epidemiol* 3, 71–77.
- Fein, G., Bachman, L., Fisher, S., & Davenport, L. (1990). Cognitive impairments in abstinent alcoholics. *West J Med* 152, 531–537.
- Feng, T. (1993). Substance abuse in pregnancy. *Curr Opin Obstet Gynecol* 5, 16–23.
- Fletcher, P. C., & Henson, R. N. (2001). Frontal lobes and human memory: insights from functional neuroimaging. *Brain* 124(Pt 5), 849–881.
- Glat, S. L., Hubble, J. P., Lyons, K., Paolo, A., Troster, A. I., Hassanein, R. E., & Koller, W. C. (1996). Risk factors for dementia in Parkinson's disease: effect of education. *Neuroepidemiology* 15, 20–25.
- Graves, A. B., Mortimer, J. A., Larson, E. B., Wenzlow, A., Bowen, J. D., & McCormick, W. C. (1996). Head circumference as a measure of cognitive reserve: association with severity of impairment in Alzheimer's disease. *Br J Psychiatry* 169, 86–92.
- Hack, M., Friedman, H., & Fanaroff, A. A. (1996). Outcomes of extremely low birth weight infants. *Pediatrics* 98, 931–937.
- Hack, M., & Taylor, H. G. (2000). Perinatal brain injury in preterm infants and later neurobehavioral function. *JAMA* 284, 1973–1974.
- Haug, H. (1987). Brain sizes, surfaces, and neuronal sizes of the cortex cerebri: a stereological investigation of man and his variability and a comparison with some mammals (primates, whales, marsupials, insectivores, and one elephant). *Am J Anat* 180, 126–142.
- Katzman, R. (1993). Education and the prevalence of dementia and Alzheimer's disease. *Neurology* 43, 13–20.
- Katzman, R., Terry, R., DeTeresa, R., Brown, T., Davies, P., Fuld, P., Rebing, X., & Peck, A. (1988). Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neurocortical plaques. *Ann Neurol* 23, 138–144.
- Larroque, B., Bertrais, S., Czernichow, P., & Leger, J. (2001). School difficulties in 20-year-olds who were born small for gestational age at term in a regional cohort study. *Pediatrics* 108, 111–115.
- Lou, H. C., Hansen, D., Nordentoft, M., Pryds, O., Jensen, F., Nim, J., & Hemmingsen, R. (1994). Prenatal stressors of human life affect fetal brain development. *Dev Med Child Neurol* 36, 826–832.
- Mori, E., Hirono, N., Yamashita, H., Imamura, T., Ikejiri, Y., Ikeda, M., Kitagaki, H., Shimomura, T., & Yoneda, Y. (1997). Premorbid brain size as a determinant of reserve capacity against intellectual decline in Alzheimer's disease. *Am J Psychiatry* 154, 18–24.
- Plassman, B. L., Welsh, K. A., Helms, M., Brandt, J., Page, W. F., & Breitner, J. C. (1995). Intelligence and education as predictors of cognitive state in late life: a 50-year follow-up. *Neurology* 45, 1446–1450.
- Rabinowicz, T., Dean, D. E., Petetot, J. M., & de Courten-Myers, G. M. (1999). Gender differences in the human cerebral cortex: more neurons in males; more processes in females. *J Child Neurol* 14, 98–107.
- Rabinowicz, T., Petetot, J. M., Gartside, P. S., Sheyn, D., Sheyn, T., & de Courten-Myers, G. M. (2002). Structure of the cerebral cortex in men and women. *J Neuropathol Exp Neurol* 61, 46–57.
- Reiss, A. L., Abrams, M. T., Singer, H. S., Ross, J. L., & Denckla, M. B. (1996). Brain development, gender and IQ in children. A volumetric imaging study. *Brain* 119 (Pt 5), 1763–1774.
- Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: a formulation and review of evidence for threshold theory. *Neuropsychology* 3, 273–295.
- Scherr, P. A., Albert, M. S., Funkenstein, H. H., Cook, N. R., Hennekens, C. H., Branch, L. G., White, L. R., Taylor, J. O., & Evans, D. A. (1988). Correlates of cognitive function in an elderly community population. *Am J Epidemiol* 128, 1084–1101.
- Schmand, B., Smit, J. H., Geerlings, M. I., & Lindeboom, J. (1997). The effects of intelligence and education on the development of dementia. A test of the brain reserve hypothesis. *Psychol Med* 27, 1337–1344.
- Schofield, P. W., Mosesson, R. E., Stern, Y., & Mayeux, R. (1995). The age at onset of Alzheimer's disease and an intracranial area measurement. A relationship. *Arch Neurol* 52, 95–98.

Snowdon, D. A., Kemper, S. J., Mortimer, J. A., Greiner, L. H., Wekstein, D. R., & Markesbery, W. R. (1996). Linguistic ability in early life and cognitive function and Alzheimer's disease in late life. Findings from the Nun Study. *JAMA* 275, 528–532.

Sowell, E. R., Jernigan, T. L., Mattson, S. N., Riley, E. P., Sobel, D. E., & Jones, K. L. (1996). Abnormal development of the cerebellar

vermis in children prenatally exposed to alcohol: size reduction in lobules I–V. *Alcohol Clin Exp Res* 20, 31–34.

Stoch, M. B., Smythe, P. M., Moodie, A. D., & Bradshaw, D. (1982). Psychosocial outcome and CT findings after gross undernourishment during infancy: a 20-year developmental study. *Dev Med Child Neurol* 24, 419–436.