Committee II
Theoretical Empiricism:
A General Rationale for
Scientific Model-Building

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INDIVIDUAL DIFFERENCES IN THE AGEING BRAIN:

COMMENTS ON STUDIES OF CEREBRAL BLOOD FLOW

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Discussion Paper on John L. Horn & Jarl Risberg

BLOOD FLOW IN THE BRAIN
AND
ADULTHOOD AGEING OF COGNITIVE FUNCTIONS

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A) Methodological Issues in Blood Flow Measurement

The measurement of cerebral metabolism and bloodflow with newly developed imaging techniques holds considerable promise for unravelling the mysteries of the working brain. Understandably research in this field is in its infancy. As yet powers of detection do not permit resolution of brain structure with precision. Neurophysiological concepts are gross; the brain tends to be divided into halves, quarters or segments and only occasionally discrete regions are considered on neuropsychological grounds. Scanning procedures may require a steady state, often for over an hour, and little is known about moment to moment fluctuations and adaptation. Often the requirement for subjects to remain still for long periods affects the type of patients selected for study. Resources are scarce and expensive and patient samples tend to be small. The effects of medication are more or less unchartered territory.

Little is known about the neuropsychological significance of blood flow changes in any given region, for example sudden increases in flow may indicate cognitive activation relevant to an ongoing task, affective reactions induced by the situation or a function of psychopathology, or interactions between these factors. Metabolic change could signify excitation or inhibition eminating from the site under detection, or conceivably activity from a far-flung region, e.g. through contralateral inhibition,

or reflect interactions between excitatory or inhibitory processes.

Techniques differ widely in their capabilities. The Xenon 133 method provides estimates of superficial cortex, i.e. a 2 cm rim from a lateral perspective of one hemisphere in the case of injection of the carotid artery, or of both hemispheres with inhalation (Horn and Risberg, 1984). Inferences must therefore be made about deep lying structures. Other techniques such as Positron Emission Tomography (PET) permit estimates of bloodflow and glucose or oxygen metabolism from transaxial slices of whole brain activity (Sheppard, Gruzelier, Manchanda et al., 1984).

B) Theoretical Issues

These techniques provide an important tool with which to investigate dynamic brain function. Historically the clinical neuropsychological test movement has tended to view the brain in static terms, whether psychologists have adopted views of strict localisation of function implicit in uses of the Halstead-Reitan battery, or views of wholism with global indices of organicity (Goldstein, 1948). Luria (1966) was one of the first to view the brain in dynamic terms and envisaged an interplay of functional systems or networks of areas sometimes topographically unrelated. This is exemplified in current theories of attention (Mesulam, 1981) where the posterior parietal cortex provides an internal sensory map, the cingulate gyrus regulates motivational

valence, a frontal component incorporating the frontal eye fields provides motor coordination, and the reticular formation regulates the requisite level of arousal. Gray's (1980) neuropsychological theory of anxiety provides another example. Blood flow studies and the estimation of covariation patterns will assist in the validation of such theories.

Activation patterns may nevertheless be at odds with neuropsychological specialisation and give a misleading impression about localisation of abilities. In research on hemispheric specialisation cognitive psychologists saw the need to make a distinction between on the one hand processes assumed to relate to brain structure and fixed to a particular hemisphere, such as the verbal functions of the left hemisphere and the spatial-perceptual functions of the right hemisphere, and on the other processes that are dynamic in their hemispheric influences such as attention and arousal. The latter may shift the focus of activity from one region to another in patterns that may be at odds with regional specialisation based on structural determinants (Cohen, 1982). This was demonstrated in our laboratory in a study of lateral brain function and anxiety (Gruzelier and Phelan, 1982). In medical students under the stress of examinations the divided visual-field processing of verbal stimuli showed a shift from the expected left hemisphere advantage, seen when under no pressure, to a right hemisphere advantage immediately before examinations (order of testing was

counterbalanced). Examination pressure was also associated with retarded electrodermal response habituation and raised scores on questionnaire measures of tension and frustration, both known to be associated with raised levels of anxiety. Thus the lateral shift was compatible with evidence of left hemisphere disruption in states of anxiety (Tucker, 1980), but would have mislead the laterality theorist unaware of the importance of dynamic state factors.

There are other conundrums associated with localising abilities in the working brain. A consensus opinion emerging from blood flow studies on hemispheric specialisation is that lateral asymmetries during psychological tasks seldom produce asymmetries and, where they do, the magnitude of the difference is trivial. In tasks involving speech comprehension and speech production not only are Wernicke and Broca's areas activated but so to are the corresponding areas in the right hemisphere. How can this be explained? Eccles (1980) reviews evidence for the extent and intricacy of homotopic projections between hemispheres. Dennenberg (1983) clearly demonstrated in rats with unilateral lesions how one hemisphere may inhibit the other, indicating that contralateral inhibition is a fundamental principle of hemisphere interactions. Implicit in this is the operation of functional connections incidental to the network involved in the formation of the behavioural response but necesssary to inhibit networks responsible for competing

responses. Returning to blood flow studies, presumably processes of both inhibition and excitation place demands on metabolism.

Then how is metabolism related to functional capacity? The common assumpton is that an increase in metabolism denotes for the psychological process in hand a functional advantage for the region most highly activated. Gur, Gur, Obrist et al. (1982) came to a somewhat different conclusion in Xenon 133 inhalation studies of the influence of gender and handedness in hemispheric asymmetries in cerebral blood flow during hemisphere specific tasks. Contrary to theory dextral women showed stronger lateralisation of blood flow than dextral men. A principle of compensation was invoked whereby metabolic demands and corresponding increases in blood flow were greater in women because they did not share the lateral advantages in cognition shown by men.

C) Horn and Risberg's Study of Blood flow in the Elderly

Horn and Risberg (1984) have made a substantive step in the application of Xenon 133 inhalation methods to the study of the neuropsychology of the ageing brain. Clearly from the scale of the study - up to the 891 subjects and 32 brain regions, 16 per hemisphere - their work is important. They acknowledge some of the methodological problems mentioned above but the psychopathological condition of their samples is unclear; state versus trait considerations have been approached by repeated

measurements across sessions, a full treatment of which will provide a useful complement to their theoretical paper which is the focus of our discussion.

Scale apart, their theoretical grasp of neuropsychology is particularly exciting, as is the innovative use of multivariate statistics in examining covariations in blood flow. They describe two brain regions where there were particularly striking declines in blood flow with increasing age in subjects mostly aged between 30 and 60 years. One was the superior frontal region, the behavioural functions of which were described as cognitive rather than affective and involved perservation and rigidity. The second was represented by middle cortex "a centre of gravity near the superior temporal, langus and breves gyri, laterally above the hippocampus and reticular formation". The behavioural functions ascribed to this region included monitoring incoming information, focussing attention, and it was also thought to represent an index of central nervous system arousal for it correlated highly with all other regions.

The functions of these regions the authors relate to the view of Horn (e.g. 1980) that ageing selectively impairs Fluid intelligence sparing Crystallised intelligence. Horn provides the following characteristics for the two types of intelligence. Fluid intelligence involves perceiving relationships, educing correlates, maintaining the span of immediate awareness in

reasoning, abstracting, concept formation and problem solving, all measured in unspeeded as well as speeded tasks involving figural, symbolic or semantic content but in which relatively little advantage accrues from intensive or extended education and acculturation. Crystallised intelligence involves similar cognitive processes, but depends on content which represents relatively "advanced education and acculturation either in the fundaments of the problems or in the operations which must be performed on the fundaments". It is usually measured with unspeeded tasks.

Evidence is not detailed by Horn and Risberg as to how the two regions relate to Fluid rather than Crystallised intelligence but it is said that blood flow patterns in the two regions "correlate with a number of variables in ways that suggest that MD (the middle region) measures an initial, very elementary form of attentiveness that progresses, if a problem becomes complex, to an involvement that is measured by SF (the superior frontal region)". The evidence for this claim will provide an interesting focus for discussion.

In view of the abilities which are good indicators of the two types of intelligence - such as Figural Relations and Inductive Reasoning in the case of Fluid intelligence, and Verbal Comprehension and Formal Reasoning in the case of Crystallised intelligence, analogies have been drawn between Performance and

Verbal IQ as measured by the Wechsler Adult Intelligence Scale. The association of Fluid intelligence with Performance IQ and Crystallised intelligence with Verbal IQ is not surprising in view of the dependency of verbal IQ on education and acculturation, and the dependency of Performance IQ on abilities that are relatively free of the influence of culture and education. In other respects the analogy is misleading - word fluency, a left hemisphere process, is a Fluid measure, while the spatial subtest of the Thurstone Primary Ability test, a right hemisphere process, measures Crystallised intelligence. Horn (1980) also concludes that the processes encompassed by the two types of intelligence "do not align in any direct way with hemisphere organisation of the brain".

D) Theories of Lateralised Deficits and Ageing

Notwithstanding, there is what Botwinick (1980) refers to as a classical ageing pattern represented by a Verbal-Performance IQ discrepancy in the direction of a decline in Performance IQ. This has provided fuel for a theory that ageing reflects bilateral impairment, but this is more extensive in the right hemisphere. The evidence for this, as will be seen, is provocative and would benefit from careful examination with blood flow measures, bearing in mind the strictures mentioned in Section B) above.

Two recent reviews have been devoted to the question of

lateralisation and ageing (Albert & Kaplan, 1980; Lapidot, 1983). Addressing first the Verbal-Performance IQ discrepancy Albert and Kaplan conclude that experiments that control for speed of performance which influences Performance IQ do not eliminate the discrepancy, however, if items are subjected to qualitative scoring criteria (see Botwinick and Storandt, 1974) then verbal and perceptual impairments are revealed. They report an unpublished dissertation by Farver (1975) in which focal damage was sought of the left and right parietal lobes. The results which indicated a disruption of visuospatial abilities supported a right parietal locus. A subsequent unpublished reanalysis by Kaplan shifted the locus to the right frontal lobe. Further support was also seen in the inability to draw objects, a difficulty also experienced by patients with right frontal lesions (Albert and Kaplan, 1980). They concluded that bilateral impairments do exist with ageing but that there is a preponderance of right frontal deficits.

Similarly Lapidot (1983) concluded in her review that there was evidence of both left and right-sided dysfunction, though the weight of evidence implicated the right hemisphere. Right-sided deficits were deduced from disabilities on tests of spatial memory, memory for faces, mental manipulation of visual information and the ability to generate imagery. Inconsistent evidence was found in a divided visual-field study of recall of matrices of letters in which older subjects were better in the

recall of left visual-field material, whereas younger subjects showed the expected right visual-field advantage (Charmon, 1981). Tasks that showed no unilateral effects included comparative tests of letter identification versus letter location, imagery generated by concrete and abstract nouns, spatial location, dichotic listening involving words or melodies and digit span. This suggests that a careful examination of left-right regional differences in metabolism may prove worthwhile, though gross comparisons of hemispheres are unlikely to produce significant effects.

Consideration of gender would also lead to a refinement of the laterality theory. The predominant but by no means unequivocal view about brain laterality and gender is that in females the left hemisphere is superior to the right, whereas in males the right hemisphere is superior to the left (e.g. Harris, 1980). If one adds to this the view that pathology affects the more vulnerable hemisphere (Flor-Henry, 1979) then a disadvantaged right hemisphere may be more characteristic of ageing women than men, while men may show either bilateral or predominantly left-sided impairments. Gender has not been considered as a confounding factor in the two reviews of lateralised deficits in ageing outlined above. Conceivably in some studies gender differences may have cancelled out the opposing laterality effects characteristic of men and women.

Studies that have mentioned gender do provide some support for the hypothesis that ageing will affect more the left hemisphere of men and the right hemisphere of women. In a test sensitive to temporal lobe damage - the Staggered Spondaic Word Test - McKoy et al. (1977) found that after correction for peripheral hearing loss (a common feature of the elderly) older men showed a decrement in right ear performance. Similarly Elias et al. (1977), in an auditory task which was described as involving competition between time and space, found bilateral impairments with ageing, yet older men were asymmetric showing a right ear disadvantage, whereas women showed a left ear disadvantage. However, conclusions were complicated by finding the opposite pattern of asymmetires in a subsequent experiment (Elias et al. 1979). Previously, consistent evidence with women was found when comparing a verbal and visual same-different task (Elias and Kinsbourne, 1974). Both sexes made more errors on the spatial task but this was especially true of women. Albert and Kaplin (1980) also reported sex differences implicating the right hemisphere in women from a task which required making accurate drawings from memory. Finally Baxter and Gruzelier (1984) found an age-related effect specific to women not men. In a haptic sorting task processing times, corrected for movement time, correlated significantly with left but not right hand times in women indicating a slowing of right hemisphere cognitive processes as women grow older. Interestingly movement times for the combined sample of men and women correlated with age with the

right hand and not the left, indicating a left hemisphere influence in the slowing of speeded movements with increasing age. Clearly investigation of lateral dysfunction with ageing must take gender into account.

E) Asymmetric Left Antero-Temporal Slow Wave Activity

Substantive evidence also exists for lateral asymmetries in electrocortical activity having an onset during late middle age. This is of particular relevance to the thesis of Horn and Risberg that a reduction in arousal is central to the ageing process. This psychophysiological measure takes the form of bursts of high voltage slow waves (1 - 7 Hz) sometimes accompanied by sharp waves and amplitude asymmetries. These were seen in about 30-50% of normal, elderly subjects as reviewed by Marsh and Thompson (1977), and have been associated with reduced blood flow in organic dementia (Ingvar and Gustafson, 1970; Obrist et al., 1970; Simard et al. 1971). According to Obrist and Busse (1965) they begin at about the age of 50 years. Marsh and Thompson conclude that 75% of the time they appear in the left hemisphere and predominantly in the anterior temporal region. A vascular basis for the slow wave activity is assumed in view of reports of a preponderance of focal vascular disturbances in the left temporal region (Hughes, 1960). It would therefore be of interest to see whether the data of Horn and Risberg show an asymmetry in this region. Nevertheless, as this is a phasic disturbance it may not be revealed in blood flow studies which require a steady

state.

Should blood flow studies prove to be revealing light would be shed on the functional significance of the unilateral slow wave bursts. Marsh and Thompson in their review concluded that "neither in middle aged nor older groups is there any correlation of this EEG abnormality with constitutional make-up or alteration in function". They list the following issues as being unrelated - handedness, seizures or aphasia, intellectual and psychiatric ratings, learning and recall, WAIS profiles. Evidence is equivocal as to whether it is associated with Verbal-Performance discrepancies (c.t. Drachman and Hughes (1971) with Obrist (1965)) though in a longitudinal study Wang, Obrist and Busse (1970) found a decline in the WAIS verbal score over a 3-4 year period. Perhaps over much is made of the failure to find neuropsychological correlates of the slow wave activity and tests have not been subtle and specific enough to reveal anomalies of phasic arousal.

F). Arousal Theory and Ageing

The evidence of Horn and Risberg of a reduction in blood flow with ageing accords with psychophysiological studies involving autonomic measures. In their review Marsh and Thompson (1977) conclude that autonomic measures of tonic and phasic arousal consistently show a reduction of activity in the elderly. More recent studies have confirmed a reduction in levels of

electrodermal activity but have not always found this to be true of responses. Nevertheless in a study just completed we have found in a comparison of mostly middle-aged cardiac patients and controls that whereas patients showed a higher incidence of orienting responses in a standard tone habituation paradigm, indicating retarded habituation, controls showed an age-ralated effect in the direction of fewer responses with increasing age (Gruzelier, Nixon, Pugh et al. 1984).

Marsh and Thompson (1977) raised a paradox when electrocortical measures were contrasted with autonomic measures - the former showed raised and the latter lowered levels of activation. Fractionation between electrocortical and autonomic measures in the direction of raised cortical and lower autonomic activity is reminiscent of findings with primates after lesions of frontal-limbic regions (Bagshaw and Benzies, 1968; Pribram and McGuinness, 1975). This type of dysfunction in ageing would be consistent with evidence of hippocampal impairments (Horn and Risberg, 1984).

G) Individual Differences and Cerebral Networks

In conclusion, if the large sample size and patient resources of Horn and Risberg signify a homogeneity in subject characteristics sufficient for the application of covariation statistics and which would permit further subdivision, it would then be of interest to compare males and females for regional

patterns of flow and in particular for differences in lateral asymmetries. Controlling for individual differences in anxiety may also reduce variance as well as clarify the influence of anxiety. From our own observations in PET studies the majority of subjects find the scanning procedure anxiety provoking. Gur (1983) has utilised this to investigate anxiety by obtaining questionnaire measures of state of anxiety in all subjects at the time of scanning. While a retrospective use of data rules out the use of anxiety measures, comparisons between repeated measures where these have been obtained (see Risberg, Maximilian and Prohovnik, 1977) may reveal first session effects due to anxiety.

Finally, the manipulation of the psychological state of the subject through task involvement has been recommended as a strategy for placing the psychological vagaries of the so called resting state under tighter control (Gur, Skolnick, Gur et al., 1983). Perhaps over much as been made of this when it is realised that engagement in psychological tasks can create additional nuisance variables in the form of stress and poor motivation. Nevertheless the psychological manipulation of blood flow patterns within the confines of steady state requirements, together with the application of covariation statistics could provide insights into cortical networks, in addition to the focal covariation patterns examined by Horn and Risberg.