Cognitive deficits in depression

Possible implications for functional neuropathology

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Background While depression is known to involve a disturbance of mood, movement and cognition, its associated cognitive deficits are frequently viewed as simple epiphenomena of the disorder.

Aims To review the status of cognitive deficits in depression and their putative neurobiological underpinnings.

Method Selective computerised review of the literature examining cognitive deficits in depression and their brain correlates.

Results Recent studies report both mnemonic deficits and the presence of executive impairment – possibly selective for set-shifting tasks – in depression. Many studies suggest that these occur independent of age, depression severity and subtype, task 'difficulty', motivation and response bias: some persist upon clinical 'recovery'.

Conclusions Mnemonic and executive deficits do not appear to be epiphenomena of depressive disorder. A focus on the interactions between motivation, affect and cognitive function may allow greater understanding of the interplay between key aspects of the dorsal and ventral aspects of the prefrontal cortex in depression.

Declaration of interest This paper was supported by an Australian National Health and Medical Research Council Program Grant (993208).

There has been a renewal of interest in testing patients with depression on a broad range of neuropsychological tasks in the last decade. It has promoted a growing awareness that, like schizophrenia and neurological disorders, mood disorders may be associated with a distinct pattern of cognitive impairment. Such impairments of cognitive function are seldom measured. This is surprising because it is easier objectively to measure memory impairment, for example, than it is to characterise other core features of depression such as the severity of depressed mood or sleep disturbance. Cognitive impairment is also likely to be a key factor affecting the subject's ability to function occupationally and, hence, the timing of his or her return to work. However, also central to current interest is the effort to link theories of cognitive neuropsychology to the anatomy and physiology of brain function. If depression is indeed a brain disease then neuropsychological impairments may lead us to the relevant neural substrate(s). In this article we aim to review the cognitive deficits reported in depression and how these deficits may reflect disruption in the anatomy and function of putative frontosubcortical neuronal pathways.

METHOD

Computerised Medline and Psycinfo searches were performed from January 1966 to September 1999 using the terms NEUROPSYCHOLOGICAL TESTING, COGNITIVE FUNCTION, DEPRESSION and DEPRESSIVE DISORDERS. Where a large number of studies had been performed, only the most methodologically rigorous are highlighted. Where there is a paucity of studies (e.g. of follow-up), those available are overviewed. This is not an all-inclusive review, and the choice of articles reflects the authors' qualitative assessment of current themes of importance in this area of research.

RESULTS

Cognitive deficits in depression

It is now commonly accepted that depression is associated with a number of deficits in episodic memory and learning (see Goodwin, 1997 for a review). This finding is consistent across most studies and appears to involve both explicit verbal and visual memory in patients with both melancholic (endogenous) and non-melancholic (non-endogenous) depression (Austin *et al*, 1999). Implicit memory tasks, on the other hand, appear to be spared (Hertel & Hardin, 1990; Denny & Hunt, 1992; Bazin *et al*, 1994; Danion *et al*, 1995; Ilsley *et al*, 1995). Temporal lobe lesions typically disrupt episodic memory; given that reductions in hippocampal volume are demonstrated in patients with major depression (Sheline *et al*, 1996) it may be that impaired mnemonic function is associated with dysfunction of the hippocampus in depression.

The initial studies examining impairment in executive tasks produced conflicting results, although, in general, significant impairment was seen in subjects with more severe depression (Friedman, 1964; Raskin *et al*, 1982; Silberman *et al*, 1983). The pattern of executive deficits described in recent reports has been relatively consistent across studies (Austin *et al*, 1992*a*, 1999; Beats *et al*, 1996; Purcell *et al*, 1997; Murphy *et al*, 1999), with a single exception (Elliott *et al*, 1996). Thus, Beats *et al* (1996), examining a more severely depressed elderly sample found these subjects to be most prominently impaired on verbal fluency and attentional set-shifting. Purcell *et al* (1997) in a study of younger out-patients with moderate depression reported no impairment on working memory, but did find impairment on measures of motor speed and attentional set-shifting, with half of the depression group failing to complete all stages of this task. The number of trials to reach criterion on the extra-dimensional component of the task (which may indicate perseveration), was similar to that seen in the elderly subjects with depression in the Beats *et al* (1996) study. These 'impaired' subjects had a higher rate of admissions for treatment of depression, suggesting that those with overall greater illness severity are more impaired on set-shifting tasks. However, the studies by Channon (1996) and Channon & Green (1999) would suggest that impairment in executive function is also present in younger (mean 20–40 years) patients with dysphoria, and those with less

https://doi.org/10.1192/bjp.178.3.200 Published online by Cambridge University Press

severe depression (mean Beck Depression Inventory (Beck, 1963) scores of 17–21).

Austin *et al* (1992*a*, 1999) examined two separate depression samples, both of which were divided into endogenous and non-endogenous subsets using narrow definitions of endogenous depression – namely the Newcastle system (Carney *et al*, 1965), with the Austin *et al* (1999) study further subdividing the samples into melancholic and non-melancholic according to the CORE instrument (Parker *et al*, 1994). Both studies revealed selective executive deficits in subjects with melancholic (endogenous) compared with non-melancholic (non-endogenous) depression. In the Austin *et al* (1999) study subjects with endogenous/melancholic depression were impaired (as in the Austin *et al*, 1992*a* study) on working memory (digits backwards) as well as on tasks heavily reliant on set-shifting (Trails B, and digit symbol substitution); in addition there was an increased perseverative response on the Wisconsin Card Sorting Task (WCST; Heaton, 1981), while tasks of inhibitory control (Stroop test (Golden, 1987), WCST set initiation and maintenance) and conceptual tasks (similarities, verbal fluency), were spared. Finally, Murphy *et al* (1999), in a study comparing the performance of subjects with depression and mania on a novel affective set-shifting task, reported that subjects with depression were impaired in their ability to shift the focus of attention (apparently corresponding to the set-shifting component of the WCST), while patients with mania were impaired in their ability to inhibit behavioural responses (apparently corresponding to the interference effect of the Stroop test). This latter study further confirms the earlier trend reported for selective set-shifting deficits in depression. The exception to this finding was the study by Elliott *et al* (1996) of middle-aged subjects with moderate, predominantly chronic depression, who demonstrated impaired ability on the Tower of London, verbal fluency and spatial working memory tasks, but intact performance on a modified and easier version of the Cambridge Neuropsychological Battery (CANTAB) set-shifting task (Robbins *et al*, 1994). It may be that this version of the task was at ceiling and unable to detect an impairment in set-shifting.

Severity of depression, depressive subtype and impact upon cognitive performance

The effect of severity of depression on neurocognitive task performance has been measured in many studies by examining the correlation between Hamilton depression scores (Hamilton, 1960) and neurocognitive task scores. Findings have, however, been conflicting. Nine studies report no correlation between task performance and depression severity (Rush *et al*, 1983; Cornell *et al*, 1984; Abas *et al*, 1990; Brown *et al*, 1994; Ilsley *et al*, 1995; Trichard *et al*, 1995; Moreaud *et al*, 1996; Palmer *et al*, 1996; Purcell *et al*, 1997) while another 11 studies do report such a correlation (Stromgren, 1977; Cohen *et al*, 1982; Fromm & Schopflocher, 1984; Wolfe *et al*, 1987; Sweeney *et al*, 1989; Peselow *et al*, 1991; Austin *et al*, 1992*a*; Bazin *et al*, 1994; Tarbuck & Paykel, 1995; Elliott *et al*, 1996; Austin *et al*, 1999), often selectively for the more demanding tasks. Correlations may be sensitive to patient selection because Hamilton scores may be confounded by whether severe scores are associated with more endogenous patterns of symptoms (see below).

The finding that subjects with depression were impaired on verbal recall while performing normally on verbal recognition (Roy-Byrne *et al*, 1986) led Weingartner to suggest that patients with depression generally had difficulty with 'effortful' as compared to 'automatic' tasks (Weingartner *et al*, 1981; Cohen *et al*, 1982; Roy-Byrne *et al*, 1986). Based on correlation findings alone, the authors hypothesised that both the motor and cognitive impairments seen in depression could be secondary to an underlying motivational deficit, rather than arising in their own right. Similarly, Bazin *et al* (1994) proposed that the dissociation between explicit (impaired) and implicit (intact) memory tasks seen in patients with depression (Hertel & Hardin, 1990; Denny & Hunt, 1992; Bazin *et al*, 1994; Danion *et al*, 1995; Ilsley *et al*, 1995) was also a result of the greater effort required for the former and the more automatic performance of the latter. The 'effortful–automatic' hypothesis has been undermined by a number of studies. Frith *et al* (1983), Wolfe *et al* (1987), Golinkoff & Sweeney (1989), Austin *et al* (1992*a*, 1999) and Brown *et al* (1994) have all reported both impaired verbal recall (an effortful task) and recognition (an automatic task) in subjects with depression. In the CANTAB's Delayed Match to Sample Task (DMST), the mnemonic encoding deficit cannot be dependent upon effortful processing alone because subjects with depression showed deficits at zero delay as well as later times (Abas *et al*, 1990; Moffoot *et al*, 1994).

The impact of depressive subtype on task performance has been explored in a small number of studies. Byrne (1977) and Cornell *et al* (1984), both using the Newcastle scale to define subjects with endogenous and non-endogenous depression, found impairment of complex reaction time in subjects with endogenous depression alone. Fromm & Schopflocher (1984), also using the Newcastle criteria, and Rush *et al* (1983) using the Research Diagnostic Criteria criteria reported that subjects with endogenous depression were more impaired on all cognitive tasks (Trails, Stroop test, visual recall and complex attention) than subjects with non-endogenous depression. The relationship between severity and depression subtype is a further confounder. Thus, while Austin *et al* (1992*a*, 1999) reported frontal deficits only in their subjects with narrowly defined (Newcastle and CORE) endogenous or melancholic depression, these disappeared after covarying for Hamilton scores (Austin *et al*, 1999), indicating that this pattern of frontal deficits was more likely to be present as a result of depression severity rather than depressive subtype. A useful probe of the effects of severity *per se* is provided by the significant diurnal variation in mood seen in many subjects with melancholia, where depressed mood is typically worse early in the day. It has been demonstrated that these subjects perform less well on most cognitive tasks (except for the DMST) in the morning compared to evening, with the opposite finding in controls (Moffoot *et al*, 1994). In summary, melancholic subtype and depression severity both appear to contribute to the neuropsychological deficits seen in subjects with depression. Some tests are highly dependent on current mood severity, others are not: differential effects of this sort may offer clues to the mechanisms and brain networks involved.

Impact of motivation, 'response bias' and 'negative cognitive set' on cognitive performance in depression

The neuropsychological deficits that are correlated with depression severity have attracted controversy. A number of researchers have applied the cognitive–behavioural paradigms of motivation, 'response bias' and 'negative cognitive set', to explain the neurocognitive impairments seen in depression. Motivation has been defined as "the ability to initiate appropriate activity either spontaneously or in response to

https://doi.org/10.1192/bjp.178.3.200 Published online by Cambridge University Press

environmental cues" (Lezak, 1995). Since the implied stimulus–reward associations are partly predicated upon the ability to experience pleasure, motivation must also in some way be closely linked to hedonic drive and, in turn, to affect. It is difficult to imagine one without the other. Our understanding of motivation is based predominantly on the study of patients with frontal lobe lesions, in whom both motivation and affect are significantly compromised, suggesting, at least in those patients, "that affect and drive (i.e. motivation) are two sides of the same coin" (Lezak, 1995). It is not clear, therefore, that to study reduced motivation is not in some sense to study depression.

A number of studies have proposed that impaired motivation in depressed patients can be measured as lack of an appropriate response to explicit reward (Miller & Lewis, 1977; Layne, 1980; Henriques *et al*, 1994), where depressed patients may not perceive reward as reinforcing because of a low hedonic capacity (Meehl, 1975; Hughes *et al*, 1985). This lack of response to reward may manifest as a response bias. Conservative response bias, or the tendency for patients with depression to require a greater degree of certainty (or reward) before they respond, has been put forward as a cause of impaired performance by some (Miller & Lewis, 1977; Henriques *et al*, 1994), but not all (Deptula *et al*, 1991; Channon *et al*, 1993) authors. Henriques *et al* (1994) in a controlled study of subjects with 'dysphoria' (defined by their score on the Beck Depression Inventory), found a lack of improvement in task performance in response to financial incentive, while response to neutral and punishment conditions was the same in both groups – implying that subjects with dysphoria were selectively less responsive to reward mechanisms than controls. This lack of response to financial incentive was also reported by Richards & Ruff (1989) in their sample of out-patients with depression. These studies did not establish how tasks varied in their sensitivity to motivation: indeed, they assumed that finding the effect for one task meant it could be generalised to all tasks.

Elliott *et al* (1997) suggested that response bias to negative feedback within the testing paradigm was associated with impaired cognitive performance in subjects with depression compared with controls. Their findings suggested that a subject's awareness of failure on one problem dramatically increased the chance of failure on the subsequent problem. The authors proposed two possible explanations: either subjects with depression demonstrate a lack of adequate response to negative feedback (with inability to expend greater effort on a subsequent task); or they have a stronger negative reaction to negative feedback – manifesting cognitively as a 'negative cognitive set' (Beck, 1963) – and perform more poorly as a result. Given that the authors submitted their data-set to many *post hoc* statistical tests, the findings were by nature, exploratory. Indeed, other studies (Purcell *et al*, 1997; Shah *et al*, 1999) using a similar paradigm in subjects with equally severe depression have not reported similar results.

Negative cognitive set (Beck, 1963) was not explicitly measured by Elliott *et al* (1997), but its effect upon cognitive performance has also been explored using tasks that test memory for negatively valenced words. Many studies have demonstrated that such words are selectively recalled over positively or neutrally valenced words, implying that the subject with depression has increased access to them (Matt *et al*, 1992).

Clearly, a motivation deficit has the potential to impair the performance of all neurocognitive tasks. That it fails to do this invites the proposition that some tasks are more sensitive to such effects than others. This section has highlighted the need to clarify the concepts before the interaction between motivation, depressed affect and cognitive function can be understood.

Recovery from depression: is there persistent neuropsychological impairment?

A small number of studies have compared the performance of subjects who have recovered from depression with that of matched controls. Using this design, Paradiso *et al* (1997) found significant neurocognitive impairment in subjects who had recovered from unipolar depression which was most marked on set-shifting tasks and not related to medication status. Marcos *et al* (1994) in a study of subjects with DSM–III–R (American Psychiatric Association, 1987) melancholia who had recovered for 3 months or more, reported persistent deficits in both immediate memory and delayed recall of visual and verbal material, and block design.

Testing before and after recovery is a potentially powerful method of identifying and distinguishing state- from trait-related cognitive deficits, but the prospective studies done to date also have methodological limitations. In particular they frequently use inadequate definitions of recovery (Sternberg & Jarvik, 1976; Jones *et al*, 1988; Peselow *et al*, 1991; Bazin *et al*, 1994; Moreaud *et al*, 1996), do not control for the potential effects of medication and electroconvulsive therapy and fail to show that task performance is within the normative range at recovery (Tarbuck & Paykel, 1995). Abas *et al* (1990) tested elderly patients with endogenous depression on a number of memory measures and reported that half of those performing poorly at baseline were still impaired at recovery in spite of improved Mini-Mental State Examination (MMSE; Folstein *et al*, 1975) scores and a lack of clinical evidence for incipient dementia and independent of medication status. In a similar sample of elderly patients, Beats *et al* (1996) also found that many, but not all deficits had remitted upon recovery: specifically, measures of simple and choice reaction times, perseveration on the set-shifting task and verbal fluency did not fully recover. Peselow *et al* (1991) in a study of patients with unipolar depression treated with imipramine for 4 weeks, reported significant improvement in all mnemonic measures in treatment responders only. They concluded that, in memory tasks at least, recovery of mood was associated with significant cognitive improvement. This finding echoed the earlier findings of a small study by Calev *et al* (1986) and that of Bazin *et al* (1994) neither of which found residual impairment in either explicit (verbal and visual) or implicit memory tasks upon recovery. In contrast, Sternberg & Jarvik (1976) reported that in endogenous subjects responding to a tricyclic antidepressant after 4 weeks, improvement in immediate memory was related to degree of depressive recovery, while performance on learning and short-term memory tasks remained impaired. Trichard *et al* (1995) in a controlled study of executive task performance in middle-aged subjects with severe depression, reported improved performance on the verbal fluency task but not the Stroop task upon recovery. Thus, at present a residual deficit in mnemonic and executive function appears to be seen in some patients with a history of depression. Its rela-tionship to crucial epidemiological variables such as age, treatment, duration and chronicity of illness and number of episodes (Kessing, 1998), remains to be more clearly determined.

https://doi.org/10.1192/bjp.178.3.200 Published online by Cambridge University Press

Relationship between age, microvascular disease and cognitive impairment in depression

Age is associated with a progressive decline in cognitive function. In particular, mental processing becomes slowed; there is poorer performance on effortful tasks; and mental inflexibility, susceptibility to distractors and perseveration become more prominent. These are the very tasks in which subjects with depression, and especially those with severe depression (endogenous or melancholic), are impaired, and thus age *per se* is a significant confounder for cognitive impairment in depression (Jorm, 1986).

Advancing age is also associated with an increase in microvascular brain disease, which appears to be particularly marked in subjects with late-onset depression (Brown *et al*, 1992). Current aetiological models of late-life depression have focused particularly on the presence of microvascular disease in deep white matter suggested by magnetic resonance imaging studies (see Hickie & Scott, 1998 for a review). Severe cognitive impairment is also frequently found in older patients with severe depression and, in a significant proportion, appears not to be fully reversible (Abas *et al*, 1990; Alexopoulos *et al*, 1993; Hickie *et al*, 1997). Many older patients have concurrent hypertension, cardiovascular and cerebrovascular disease, and longitudinal studies suggest that patients with depression with these medical risk factors may be at increased risk of cognitive impairment and/or dementia (Hickie & Scott, 1998 for review). Thus, some older patients with persistent cognitive deficits due to treatment-resistant depression may have a comorbid incipient vascular dementia.

A number of studies have examined the relationship between magnetic resonance imaging and cognitive task performance in older subjects with depression, and all report a significant correlation between the presence of deep white matter hyperintensities in subjects with late-onset depression and poorer cognitive task performance, in particular on executive and psychomotor tasks (Hickie *et al*, 1995; Lesser *et al*, 1996; Kramer-Ginsberg *et al*, 1999). Although microvascular pathology, which in some cases is associated with vascular dementia, may account for the persistent cognitive deficits seen in older subjects with late-onset depression, such processes currently seem unlikely to contribute to the persistent cognitive deficits reported in many younger (i.e. under 60 years old) subjects with depression. However, we do not yet understand the neurobiological consequences of severe depression. It remains possible that there are vascular sequelae that we can only see with available technology when expressed in the ageing brain. Alternatively there may be vascular factors that predispose to depression in severe early-onset cases or may even mediate the effects of precipitating life events.

DISCUSSION

Methodological limitations of cognitive testing in depression

There are a number of significant limitations associated with the use and interpretation of standard neurocognitive testing in psychiatric disorders such as depression. While it is easy to equate a deficient neurocognitive function with the location of a neuroanatomical defect,

> "many putatively 'localising' neuropsychological procedures were derived from studies of patients with focal lesions . . . they reflect a view of brain–behaviour relationships based upon vascular anatomy . . . whether this understanding of cerebral localisation applies to less focal diseases remains to be determined" (Caine, 1986).

Most cognitive tasks tap a number of cognitive domains, making it difficult to tease out the primary functional deficit associated with impairment on any one task. The WCST, which has been the classic tool to detect a frontal lesion, exemplifies a number of these issues. In particular, it relies on examiner feedback for its performance and assesses several key cognitive domains: shifting the sorting rule when negative feedback to a previous positive stimulus–reward association occurs; memorising previous rules to ensure efficient rule testing; and establishing or rejecting rules by deductive reasoning (Dehaene & Changeux, 1991). The use of properly constructed test batteries assessing a broad range of functions in order to allow for assessment of patterns of impairment may go some way to circumventing this problem but it is unlikely to solve it (Keefe, 1995). This is particularly the case for executive function, where the nature of the neuropsychological construct itself remains controversial. Indeed there is strong evidence that the general factor, or Spearman's *g*, which identifies covariation between performance on many tests, may be the critical measure of frontal lobe function (Duncan *et al*, 1995).

Finally, while most neurocognitive tasks are designed to eliminate or minimise the effects of reward and reinforcement, it is not possible to do this for executive tasks that are dependent on feedback for their performance. The structured nature of testing may mask deficits in motivation, self-monitoring and planning which often contribute to the clinical presentation associated with depression.

Neurocognitive 'double dissociations' and the putative pathogenesis of depression

The gold standard in any attempt at localisation of neuropathophysiology by means of neurocognitive testing is the identification of mutually exclusive profiles of cognitive impairment or 'double dissociations', which are in turn linked with focal anatomical lesions (Gazzaniga *et al*, 1998). The double dissociation method has been a powerful tool in identifying different domains of prefrontal function in animal lesion studies (Dias *et al*, 1996; Rolls, 1996). In humans, this method is most applicable to the study of subjects with either focal brain lesions or relatively focal neuropathology such as Parkinson's disease or Huntington's chorea. In complex disorders such as depression, the assumption that impaired neurocognitive function will reveal the nature of the neural defect underlying the disorder remains speculative.

While double dissociations are more difficult to demonstrate in subjects with functional psychiatric disorders, there is an emerging body of work which suggests that this may be feasible. Austin *et al* (1999), using a battery with a large number of frontal tasks, demonstrated a dissociation between two sets of key frontal domains: set-shifting and working memory on the one hand, and inhibitory control on the other. Human lesion (Grattan *et al*, 1994) and imaging (Courtney *et al*, 1997) work has suggested an association between the dorsolateral prefrontal cortex and frontal cognitive deficits in depression, with a relative sparing of lateral orbitofrontal and anterior cingulate regions which have been associated with inhibitory control as reflected by performance on the Stroop task (Pardo *et al*, 1990; Bench *et al*, 1993). Such hypotheses require specific testing in activation studies with functional imaging.

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Integrating the neurocognitive and affective manifestations of depression into a functional neuroanatomical framework

There is now significant evidence, both from animal and human studies, suggesting the existence of distinct, parallel functional networks or loops linking prefrontal and subcortical regions (Alexander *et al*, 1986, 1990; Cummings, 1993). Disruption in several of these functional networks has now been implicated in the pathogenesis of a number of psychiatric disorders including major depression (Austin & Mitchell, 1995).

It was originally hypothesised (Cummings, 1993) that patients with depression have impaired function in the limbic loop with effects upon the affective, autonomic and vegetative domains. This has been partially supported by a number of imaging studies suggesting that some regions functionally linked to the anterior cingulate (part of the limbic loop), and the subgenual prefrontal cortex (PFC), are key functional regions modulating affect in depression (Austin *et al*, 1992*b*; Drevets *et al*, 1997; Mayberg *et al*, 1997). Drevets *et al* (1997) demonstrated significant reduction in both perfusion and, more intriguingly, brain volume in the subgenual region in patients with unipolar and bipolar depression. Finally, Goodwin *et al* (1993) and Mayberg *et al* (1997) both demonstrated normalisation of perfusion in the anterior cingulate upon recovery.

Findings from activation studies in normal control subjects and subjects with depression are strongly suggestive of a close integration between the dorsolateral prefrontal cortex (DLPFC) (implicated in the set-shifting deficits of depression described above) and the subgenual cingulate in depression. Thus, Teasdale *et al* (1999) reported in normal subjects that certain components of the medial prefrontal cortex (including the anterior cingulate) appear to be involved in the cognitive induction of a negative affect, thereby implying close integration between the dorsolateral and limbic circuits. Mayberg *et al* (1999) examined the impact of negative mood induction, both in normal control subjects and those subjects who had recovered from depression, on cerebral perfusion. Induced sadness was associated with an increase in subgenual cingulate cerebral blood flow and a decrease in DLPFC, while recovery from depression was associated with the reverse pattern. Intriguingly, an earlier lesion study by Bechara *et al* (1996) demonstrated that patients with ventromedial lesions had relatively preserved cognitive function, except for decision-making, which was impaired when this relied upon the ability to attach emotional salience to the task situation. Their findings, like those of Teasdale *et al* (1999) and Mayberg *et al* (1999), suggest that affect and cognitive function may be anatomically linked at the level of the ventromedial or orbitofrontal regions. Exactly how this maps onto the reciprocal interaction between two key prefrontal regions (dorsolateral and orbitofrontal) and their frontal subcortical connections remains a challenge. Nevertheless, in light of these findings, the initial proposal that the frontosubcortical networks (Alexander *et al*, 1986, 1990) essentially operate independently needs to be revised.

Are these neuropsychological deficits simply epiphenomena of depression?

The commonly held view that neuropsychological deficits in depression are simply epiphenomena of age, poor motivation, inattention or response bias now appears somewhat dated. Correlational studies evaluating the impact of age, task difficulty and depression severity upon task performance in depression partially favour the effortful–automatic hypothesis. What such a finding may mean remains uncertain. One view is simply an extension of the epiphenomena perspective: if patients feel unwell they will not try so hard. However, this fails to acknowledge that the subjective basis of all experience, including action, is neuronal. An increased sense of effort will have a neurobiology. A possible explanation for this is that failure of executive function in depression may be closely related to an increased sense of subjective effort that involves the prefrontal cortex.

A small number of studies indicate persistent cognitive impairment upon recovery in mood disorder, as noted above. These findings are reported in all age groups, although more frequently in older subjects. Thus, while psychosocial explanations of mood disorder are often uncritically accepted, the presence of neuropsychological deficits is important evidence that enduring brain abnormalities are implicated in the aetiology of depressive disorder. If cognitive impairment were simply secondary to the severity of depressed mood, then it would be expected to fully recover upon remission of the episode, and certainly would not be expected to appear in young subjects with dysphoria (mild depression).

Do these cognitive deficits help us identify the functional neuropathology of depressive disorders?

If cognitive deficits are intrinsic expressions of the brain changes in depressive illness, and we believe they are, can they help us identify the functional neuropathology of depressive disorders? The consistent impairments of memory function, which are not dependent on the acute mood changes associated with diurnal mood variation when tested using almost purely mnemonic tests (Moffoot *et al*, 1994), suggest that as we learn more about memory mechanisms in humans we shall learn more about depression. Selective set-shifting deficits – both on cognitive and affective set-shifting tasks – are also assuming an increasing interest in depression. Restricted lesions of the ventromedial prefrontal cortex have profound effects upon executive function, the recognition of emotion in others and, probably, upon the experience of mood (Damasio, 1994; Rolls *et al*, 1994; Hornak *et al*, 1996). The apparent localisation to quite a small brain area of a critical link between affect and cognition comes as something of a surprise, but it is supported by a number of functional imaging studies and by some recent neuropsychological studies in depression (Murphy *et al*, 1999; Austin *et al*, 1999).

ACKNOWLEDGEMENTS

We are most grateful to Professor Perminder Sachdev for his excellent comments on an earlier manuscript and to Professor Gordon Parker for his editorial overview.

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CLINICAL IMPLICATIONS

- Mood lowering and cognitive impairment deserve to be considered as comparably important manifestations of depressive disorder.
- Formal cognitive testing could be a useful adjunct in the clinical evaluation of patients with depression, both at index episode, but more particularly upon recovery.
- Where microvascular disease or incipient dementia may account for the cognitive deficits seen in late-onset depression, magnetic resonance imaging could be a useful tool in diagnostic clarification.

LIMITATIONS

- Cognitive activation imaging studies in depression are not covered in this review.
- The article is selective in its focus and does not provide an exhaustive review of all cognitive studies in depression.
- The specificity of cognitive deficits seen in depression is not discussed in this review, that is, a comparison between depression and other psychiatric disorders is not drawn.

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(First received 23 December 1999, final revision 28 June 2000, accepted 10 July 2000)

https://doi.org/10.1192/bjp.178.3.200 Published online by Cambridge University Press