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Review Article

Neuropsychological dysfunction in bipolar affective disorder: a critical opinion

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Data from the imaging literature have led to suggestions that permanent structural brain changes may be associated with bipolar disorder. Individuals diagnosed with bipolar disorder display deficits on a range of neuropsychological tasks in both the acute and euthymic phases of illness, and correlations between experienced number of affective episodes and task performance are commonly reported. These findings have renewed interest in the neuropsychological profile of individuals with bipolar disorder, with deficits of attention, learning and memory, and executive function, asserted to be present. This paper critically reviews five different potential causes of neurocognitive dysfunction in bipolar disorder: (i) iatrogenic, (ii) acute functional changes associated with depression or mania, (iii) permanent structural lesions of a neurodegenerative origin, (iv) permanent structural lesions that are neurodevelopmental in origin, and (v) permanent functional changes that are most likely genetic in origin. Although the potential cognitive effects of residual symptomatology and long-term medication use cannot be entirely excluded, we conclude that functional changes associated with genetically driven population variation in critical neural networks underpin both the neurocognitive and affective symptoms of bipolar disorder. The philosophical implications of this conclusion for neuropsychology are briefly discussed.

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Background

Bipolar disorder is a pathological disturbance of mood, typically characterized by oscillating manic and depressive states (1). The aetiology of the disorder is unknown but twin, adoption and epidemiological studies are suggestive of a strong genetic influence. First-degree relatives of bipolar probands have an elevated risk of developing both unipolar (about threefold) and bipolar depressive episodes (approximately 10-fold) (2). Twin and adoption studies suggest that this elevated illness risk has a genetic basis with heritability scores of between 60 and 85% widely reported in the literature (2, 3).

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The nature of the cognitive deficit: functional or structural?

The neurocognitive functioning of people with bipolar disorder has become a focus of recent research, but the *Grundstörung* (fundamental disturbance) has yet to be identified. A large number of deficits are asserted to be characteristic of the disorder. Impairments of working memory (4), sustained attention (5, 6), 'focusing-execution' (7), abstract reasoning and visuomotor skills (8), verbal memory (9–11), verbal fluency (12), cognitive flexibility (13, 14), visuospatial ability (15), and general cognitive function (16–18) have all been reported, even in the euthymic phase of the illness.

It is unclear whether the cognitive deficits of patients with bipolar disorder are reflective of (i) iatrogenic or alcohol effects, (ii) temporary functional changes – that is a product of fluctuations in mood, (iii) degenerative structural brain changes, (iv) permanent structural lesions of a

neurodevelopmental aetiology, or (v) permanent or at least enduring functional alterations of the neural networks underpinning affect and cognition. We discuss the merits of position (i) first.

Alcohol abuse, which is common in bipolar disorder (19), occurring in 30–50% of cases (20), can lead to significant cognitive deficits (21), particularly on tasks sensitive to memory and executive functioning (22, 23). van Gorp et al. (9) found that length of illness was predictive of greater cognitive impairment in a group of bipolars with alcohol dependence than in a non-alcoholic group. The bipolar group without alcohol dependence did not differ significantly from controls on measures of executive function (9). Zubieta et al. (24), Harmer et al. (6), and Cavanagh et al. (11) however, reported significant deficits in memory, speed of information processing, executive functioning, and motor co-ordination in a non-substance abusing group of euthymic bipolars. Although in many cases the acute effects of alcohol or drug intoxication have been ruled out (10, 18, 25), the effects of past exposures have not been taken into account, and this remains a weak point in the literature.

Donaldson et al. (26) raise the possibility that the cognitive dysfunction is iatrogenic. Lithium has been reported to have adverse effects on memory and psychomotor functioning (27–29), while valproate and carbemazepine may cause attentional difficulties (30). Neuroleptics have been associated with sustained attention and visuomotor speed deficits (31), and benzodiazepines are known to interfere with memory (32). Zubieta et al. (24) found that performance on the Wisconsin Card Sorting Test (WCST) was negatively correlated with years of exposure to antipsychotic drugs. Crews et al. (33) found no significant neuropsychological deficits in a young, unmedicated group of women with major depression, a result that the authors partly attribute to the effect of psychiatric medications.

In a longitudinal study, however, Engelsmann et al. (34) failed to detect evidence of cognitive decline over a 6-year period in a sample of bipolar patients treated with lithium. Comparison of long-term and short-term lithium treatment groups also failed to yield significant memory score differentials (34). More recent work (35, 36) indicates that lithium and sodium valproate, rather than impacting negatively on cognition, actually exert a neuroprotective effect on neuronal tissue.

As noted by Murphy and Sahakian (37), and Bearden et al. (38), however, patients with bipolar disorder are often treated with complex combinations of mood-stabilizers, antidepressants, antipsychotics and anxiolytics, and the combinatorial effects of these drugs on cognition is a matter of speculation. Patients with bipolar disorder are also at an increased risk for suicide, and suicide attempts are common (39, 40). We have anecdotal evidence to suggest that certain patterns of cognitive impairment may be related to medication overdose.

Clearly this is a topic worthy of further investigation, although in the light of reported cognitive deficiencies in medically naïve at-risk individuals (see below) we think that the iatrogenic position cannot explain all the data. Theoretically, the effects of medication could be controlled for by examining a drug-free cohort of patients, however this would either raise ethical concerns or the sample in question would be unrepresentative of the general bipolar population. These data suggest that one of positions (ii)–(v) discussed above would provide a better explanation for the cognitive deficits under consideration.

In the following section, position (ii) – the possibility of temporary functional deficits – is discussed. Numerous studies have demonstrated the presence of neuropsychological deficits in acutely depressed patients, with verbal and visual memory as well as executive function emphasized by most authors (41–47). The decrement in cognition has been variously attributed to reduced motivation (44, 48), attenuated attentional capacity (45), impaired concentration (49), intrusive thoughts (50), and slowness of mentation and movement (51). Anxiety or stress has been shown to adversely affect cognition in both humans and animal models by decreasing working memory function (52). The physiological basis of this effect is unclear although a number of studies have suggested that the effect may be mediated by hypercortisolaemia (11, 53–55). Consistent with these hypotheses, neurocognitive function has been asserted to revert to normal on clinical recovery (47, 52, 56). Mania is understudied in comparison with depression, but attention and executive dysfunction appear to be salient features of the mood state (37, 57–59).

What are the neurophysiological correlates of these putative cognition impairing mood states? Functional imaging studies of depression have consistently reported hypofrontality, with the dorsolateral prefrontal cortex (60), the subgenual cortex (61, 62), the anterior cingulate (63, 64), and the medial prefrontal cortex (65, 66) all implicated. Blumberg et al. (67) contend, however, that the weight of evidence points to decreased dorsal prefrontal cortex and anterior cingulate gyrus activation, but increased activity of the ventral

prefrontal cortex during depression. Mania is associated with the opposite pattern with decreased ventral and increased dorsal activity of the prefrontal cortex (68, 69). There also appears to be a degree of lateralization to these changes in cortical metabolism. Relative reductions in left hemisphere activity are correlated with depression, while right hemisphere dysfunction is more pronounced in the manic state (68, 69). These data are congruent with the hypothesis of Davidson et al. (70) that the left prefrontal region is involved in appetitive functions, while the right hemisphere mediates the maintenance of goals requiring behavioural inhibition.

Similarly, remission of depressive symptoms or treatment with antidepressants is associated with increased regional blood flow to the dorsolateral and medial prefrontal cortex, including the anterior cingulate gyrus, and decreased glucose metabolism of the ventral prefrontal cortex (71–73). These changes in glucose metabolism are postulated to reflect changes in local synaptic activity and neurotransmission (74) and presumably account for some of the cognitive abnormalities present during acute depressive or manic episodes.

On the basis of this array of functional neuroimaging data, Mayberg and colleagues have proposed that depression-associated cognitive deficits result from a right-hemisphere disturbance of attentional control, characterized by limbic activation with hypometabolism of the dorsal prefrontal cortex, cingulate gyrus, and the paralimbic cortex (75, 76). Similarly, Blumberg et al. (67) have hypothesized that the distractibility and behavioural dysregulation accompanying mania is a result of the heightened activity of a left hemisphere prefrontal cortical–subcortical system that includes the caudate and anterior cingulate. Davidson et al. (70) suggested that hypoactivation of the dorsal anterior cingulate gyrus produces impaired modulation of attention and executive function while hypoactivation of the ventral anterior cingulate produces hypoarousal, anhedonia and other affective symptoms of depression. Although the details of its neuroanatomy are still a matter of debate, it is clear that the integrity of this frontostriatal system is necessary for the flexible and adaptive behaviour that is characteristic of our species (77).

Additional evidence for the importance of the frontostriatal system in bipolar disorder is derived from studies that have specifically identified attentional impairments in people with bipolar disorder. The dorsolateral prefrontal cortex, anterior cingulate and other components of the frontostriatal system play a crucial role in attention processing (78). Wilder-Willis et al. (79), Liu et al. (80), Harmer et al. (6) and Clarke et al. (5) all reported bipolar-associated performance decrements on continuous performance tasks – a measure of sustained attention (81). It is also interesting that attention deficit hyperactivity disorder (ADHD) in childhood is often the first sign of a bipolar diathesis (82). A longitudinal study of 134 bipolar offspring (82) found that approximately one third of the sample evinced behavioural and attention problems. Faraone et al. (83) hypothesized that families with co-occurring ADHD and bipolar illness represent a specific genetic subtype of early onset manic depression.

The state-dependent functional disturbance model (position ii) is however challenged by data which suggest that neurocognitive deficits are not simply a by-product of the mood disturbance, but are also apparent in the euthymic phase of the illness (4, 5, 11, 84). The literature examining neurocognitive function in euthymic individuals with bipolar disorder is summarized in Table 1. Of the 40 studies presented in Table 1, only three failed to detect cognitive impairment in euthymic bipolar patients, producing at first glance strong evidence for the presence of permanent trait deficits in manic depressive individuals. These data favour positions (iii), (iv) or (v) mentioned above.

Ferrier et al. (4), Rubinsztein et al. (84) and Clark et al. (5) point out, however, that study participants who are labelled as euthymic, may in fact display residual affective symptoms or may not exhibit enough symptoms to meet the DSM-IV criteria for depression or mania. This is especially true in the older literature, in which the use of the term 'euthymic' is vague and appears to be synonymous with the absence of psychosis. There is evidence to suggest that in the period after remission from an acute affective episode, the individual experiences increased emotional reactivity and mood lability (66, 85). Scott et al. (86) remarked on the fact that 30% of their sample had Beck Depression Inventory scores >10 (indicative of depression) despite being rated as euthymic by clinicians. Thus we suggest that mood-associated functional changes cannot be entirely dismissed as a possible cause of the cognitive deficits associated with bipolar illness.

Data from structural imaging studies

A potential criticism of our position is that we have introduced a false dualism by artificially differentiating between structural and functional effects. The past few years have witnessed a surge in papers describing various structural changes in the brains

Table 1. Neuropsychological impairments reported in euthymic persons with bipolar disorder

Study	Sample size (patient sample + control)	Mean age (BP)	Measure of euthymia	Impaired domain	Tasks evincing impairment	Tasks not evincing impairment
Zalla et al. (145)	37 (BP) + 20 (C)	36.6 (8.3)	<16 MADRS and <7 BRMRS	Inhibition	Stroop	TMT, WCST, COWAT
Martinez-Aran et al. (59)	44 + 30	39.6 (9.5)	<9 Ham-D and <7 YMS	Executive function and verbal memory	WCST, Digits, Stroop, CVLT	COWAT, WMS
Donaldson et al. (26)	43 versus normative data	42.9 (11.1)	<10 Ham-D and <10 MRS	Visual and verbal memory	Subtests of the WMS	Subtests of the WMS
Martinez-Aran et al. (190)	49 (BP) + 49 (Schiz)	38.1 (9.8)	<9 Ham-D and <7 YMS	Executive function	COWAT, TMT and WCST	NA
Swann et al. (191)	22 + 35	33 (8)	SADS-C	Impulsivity	BIS	CPT (IMT)
Liu et al. (80)	68 + 345	36.0	BPRS, Ham-D, YMS	Sustained attention	CPT[a]	NA
Harmer et al. (6)	19 + 19	38.4 (2.6)	<8 Ham-D <8 YMS	Sustained attention	Non-working memory CPT	Working memory CPT
Clark et al. (5)	30 + 30	35.9 (11.0)	<8 Ham-D and <8 YMS	Sustained attention	RVIP (CPT)	TOL, IGT, CVLT, spatial working memory
Cavanagh et al. (11)	20 + 20	43.8 (14.2)	<7 Ham-D and <2 MMS	Verbal learning and memory	CVLT	COWAT, HSCT, BADS, Stroop
El-Badri et al. (118)	29 + 26	30.7 (6.1)	BDI and clinical judgement	Visual planning and memory, set-shifting working memory	TOL, DSST, Digits, TMT-B	COWAT
Wilder-Willis et al. (79)	14 + 12	33 (7)	<6 YMS	Sustained attention and fine motor skills	CPT and G-PEG	Digits
MacQueen et al. (192)	28 + 28	42.2 (12.3)	<8 Ham-D and <6 YMS	Visual information processing	VBM tasks	NA
Zubieta et al. (24)	15 + 15	39 (13)	<6 Ham-D and <4 YMS	Verbal learning and memory, executive function, motor speed	PALT, WCST, Stroop, BTI	WMS (visual memory), COWAT CPT, Digits
Thompson et al. (193)	20 + 20	Not given	<9 Ham-D and <9 YMS	Strategic control of working memory	SOPT	NA
Thompson et al. (194)	20 + 20	Not given	<9 Ham-D and <9 YMS	Strategic control of working memory	Digits (B), Stroop	Digits (F), COWAT, TMT-B
Thompson et al. (195)	30 + 30	Not given	<9 Ham-D and <9 YMS	Verbal learning and fluency	RAVLT, COWAT	NA
Rubinsztein et al. (84)	18 + 18	42 (2)	<8 Ham-D and <8 on YMS	Visuospatial memory	Spatial recognition memory and DMTS (CANTAB)	Set-shifting, TOL (CANTAB)
Scott et al. (86)	41 + 20	44.7 (10.5)	<7 Ham-D and <20 MSS	Thinking ability (social problem solving)	MEPS	Memory (autobiographical)
Rossi et al. (196)	40 + 64	35.7 (11.67)	Not specified	No deficit	NA	WCST
Ali et al. (8)	26 versus normative data	40.2 (10.9)	Outpatients: not specified	Executive function, attention, visual and verbal memory	WCST, TMT (A + B), Stroop, CPT, VCT, CVLT	COWAT
Krabbendam et al. (18)	22 + 22	47.7 (8.3)	Clinical judgement, average Ham-D = 3.4, YMRS = 0.77	Executive function, verbal fluency	RAVLT, TMT, LDST	Stroop, COWAT
Ferrier et al. (4)	41 + 20	44.8 (10.6)	<8 Ham-D and <20 MSS	Executive control of working memory	COWAT, Digits (B), TMT (A + B)	RCF, Digits (F), TOL, VCT

Table 1. Continued

van Gorp et al. (10)	31 + 18	49.6	<7 Ham-D and <6 YMS	Declarative verbal memory	CVLT	PRT and SMT (procedural memory)
Kessing (17)	28 + 58	58.5 (14.2)	<8 Ham-D	General cognitive dysfunction	CAMCOG, MATTIS, GBS, GDS[a]	NA
Atre-Viadya et al. (25)	36 versus normative data	50 (14)	Clinical judgement and <120 MDRS	Verbal memory and learning, fluency and visual-spatial function	COWAT, CVLT, RPM	NA
van Gorp et al. (9)	25 + 22	52.2	<7 Ham-D and <6 YMS	Verbal memory, set-shifting	CAVLT, WCST	RCF, COWAT, Stroop, TMT (A + B)
Paradiso et al. (124)[b]	31 (mixed BP + UP) + 19	57 (11.3)	<14 Ham-D and <16 MBRS	No deficit (BP only)	NA (BP only)	TMT (A + B), Stroop, CERAD, DSST
Hawkins et al. (14)[c]	22 + 26	41.9 (12.7)	Outpatients with average score of 11.4 on SCL-90-R	Executive function, incidental learning and motor execution	TMT-B, DSST (WAIS)	Digits (F + B), TMT-A, COWAT, WAIS (Sim + Arith), BNT
Tham et al. (13)	26 versus normative data	47.3	Not specified	Psychomotor function, verbal learning and memory, visual-spatial skills	TMT (A + B), CDVLT, KBDT	NA
Docherty et al. (197)	24 + 23	43 (13)	Relatively remitted: not specified	Executive function	COWAT	CPT, TMT-B
McKay et al. (56)	45 (mixed UP + BP) versus normative data	63.8 (chronic group)	MADRS and clinical judgement	Executive function and memory	RBMT + COWAT (chronic, illness only)	NA
Jones et al. (7)	26 + 16	35.6 (11.1)	Average BHS depression = 4.7, mania = 1.6	Visual memory, executive function and attention	VCT, TMT (A + B), RCF, block design	CPT, WAIS (Vocab, Sim + Com), Babcock Story, BSR
Coffman et al. (198)	30 + 30	32 (6.2)	Not specified	Executive function, memory, visual-spatial and motor performance	TPT, HRB (categories), TMT (A + B), WCST, WMS (non-verbal)	WMS (verbal memory), verbal IQ
Waddington et al. (199)	40 versus normative data	41.6 (14)	Not specified	Executive function	TMT (A + B)	NA
Sapin et al. (15)	20 + 20	36.75 (2.05)	Clinical judgement	Non-verbal memory	GCT	Block design, BVR, digit span, face recognition
Kerry et al. (200)	23 versus normative data	No data	Not specified	No deficit	NA	Verbal and visual memory (WAIS)
Lund et al. (201)	50 versus normative data	52	Not specified	Not specified	Digits (B)	Story recall, Digits (F), Stroop
Asarnow and MacCrimmon (202)	20 + 20	46.3 (13.2)	Clinical judgement and GAS and PSS	Sustained attention and visual information processing	Span of apprehension (CPT)	NA

Savard et al. (203)	15 + 42	37 (2.4)	Average 3.3 BHS	Executive function	Category subtest of HRB [older (>40) patients]	HRB (young group)
Friedman et al. (204)	13 versus normative data	62.4	Not specified	General cognitive function	HRB (older group)	HRB (young group)

BADS = Behavioural Assessment of the Dysexecutive System; BDI = Beck Depression Inventory; BHS = Bunney-Hamburg Scale; BIS = Barrat Impulsiveness Scale; BNT = Boston Naming Test; BP = bipolar disorder; BPRS = Brief Psychiatric Rating Scale; BRMRS = Bech-Rafaelsen Mania Rating Scale; BSR = Buschke Selective Reminding Task; BTI = Bead-Tap and Imitation; BVR = Benton Visual Retention Test; C = controls; CAMCOG = Cambridge Cognitive Examination; CANTAB = Cambridge Neuropsychological Test Automated Battery; CAVLT = California Verbal Learning Test; CDVLT = Claeson-Dahl Verbal Learning Test; CERAD = word list memory test; COWAT = Controlled Oral Word Association Task; CPT = Continuous Performance Test; Digits (F + B) = Digits (Forward and Backward); DMTS = Delayed Matching to Sample; DSST = Digit Symbol Substitution Test; GAS = Global Assessment Scale; GBS = Gottfries-Brane-Steen Dementia Rating Scale; GCT = Gestalt Completion Task; GDS = Global Deterioration Scale; G-PEG = Grooved Pegboard; Ham-D = Hamilton Rating Scale for Depression; HRB = Halstead-Reitan Battery; HSCT = Hayling Sentence Completion Test; IGT = Iowa Gambling Task; IMT = Intermediate Memory Task; KBDT = Koh's Block Design Test; LDST = Letter Digit Substitution Task; MADRS = Montgomery-Asberg Depression Rating Scale; MBRS = Manic Behavior Rating Scale; MDRS = Mattis Dementia Rating Scale; MEPS = Means-Ends Problem-Solving; MMS = Modified Manic State Rating Scale; PALT = Paired Associates Learning Test; PPT = Purdue Pegboard Test; PRT = Pursuit Rotor Task; PSS = Psychiatric Status Schedule; RAVLT = Rey Auditory Verbal Learning Test; RBMT = Rivermead Behavioural Memory Test; RCF = Rey Complex Figure; RPM = Raven's Progressive Matrices; RVIP = Rapid Visual Information Processing; SADS-C = Schedule for Affective Disorders and Schizophrenia (Change Version); Schiz = schizophrenia; SCL-90-R = Symptom Checklist 90-Revised; SMT = Star Mirror Tracing Task; SOPT = Self-Ordered Pointing Task; SRB = Synonym, Reasoning and Block Test Battery; TMT = Trail Making Test; TMT-A = Trail Making Test Part A; TMT-B = Trail Making Test Part B; TOL = Tower of London; TPT = Tactile Performance Test; UP = unipolar depression; VBM = Visual Backward Masking Task; VCT = Visual Cancellation Task; WAIS = Wechsler Adult Intelligence Scale (subtests: Arith = Arithmetic; Com = Comprehension; Sim = Similarities; Vocab = Vocabulary); WCST = Wisconsin Card Sorting Test; WMS = Wechsler Memory Scale; YMS = Young Mania Rating Scale.

[a]Performance was worse in the inpatient than the outpatient group.

[b]Deficits only reached statistical significance in the unipolar group.

[c]This study was included because the authors reported that there was no relationship between the depression score and cognitive performance.

of schizophrenics and manic depressives. In the following section we briefly review the imaging literature, and defend our contention that the case for permanent structural lesions in bipolar affective illness (positions iii and iv) remains unproven.

A wide range of anatomical abnormalities have been reported in bipolar disorder, although the literature is plagued with abundant failures to replicate previously reported associations. Volume reductions (and occasionally increases) of the frontal cortex and anterior cingulate gyrus, temporal lobe, hippocampus, amygdala, basal ganglia, thalamus, and cortical grey matter are commonly but inconsistently reported (38, 87, 88). The best replicated morphological changes appear to be ventriculomegaly of the lateral and third ventricle, and hyperintensities of the sub-cortical white matter (38, 89).

Salokangas et al. (90), Friedman et al. (16) and Steingard et al. (91) reported ventriculomegaly in psychotic manic depressives, a general sample of bipolar subjects, and hospitalized children with depressive disorders respectively. Strakowski et al. (92) detected significantly larger third and lateral ventricle volumes in multiple-episode bipolars compared with their first-episode counterparts, and argue that lateral ventriculomegaly may be a pathological marker of the effects of multiple affective episodes on brain tissue. On the basis of their review of the literature, Bearden et al. (38) concluded that approximately 10–30% of patients with bipolar disorder present with abnormally large ventricles, although the relationship with clinical outcome remains unclear.

White matter intensities (WMH) as evinced by T2-weighted magnetic resonance imaging (MRI) are known to increase with age and are associated with conditions such as hypertension and arteriosclerosis, indicating an ischaemic aetiology (38). Figiel et al. (93) announced that they had found WMH in two bipolar patients in their mid-twenties. Botteron et al. (94) discussed a case of a 14-year-old patient with bipolar disorder who displayed pronounced WMH on imaging. In a sample of eight bipolar children, the same group reported WMH in two of the subjects (95). Strakowski et al.'s (96) 18 strong first episode sample of patients with mania exhibited 1.7 times as many WMH as controls, but the difference was not statistically significant. Aylward et al. (97) and Dupont et al. (98), however, both uncovered significantly higher percentages of WMH in their middle age bipolar samples relative to matched control groups, and Lyoo et al. (99) reported a WMH prevalence of 2.4 and 17.9% in their 42 and 56 strong schizophrenia and bipolar samples respectively. Pillai et al. (100) uncovered an even stronger effect: Ten of 15 of their sample of adolescent bipolar patients showed evidence of WMH, approximately double the prevalence of schizophrenic or control subjects. Most of the WMH reported in the literature are located in the subcortical white matter of the frontal lobes and basal ganglia (89, 99). Videbech (89), Soares and Mann (87) and Sheline (88) postulated that the location of the WMH is suggestive of a defective frontal-basal ganglia circuit, evoking parallels with the frontostriatal circuit implicated in the functional studies of affective illness described above.

Bearden et al. (38) reviewed the association between leuko-araiosis and cognitive deficits in bipolar disorder. WMH correlated with lowered frontal lobe metabolism, ventriculomegaly, and deficits on tasks that required complex or speeded information processing and attention, raising parallels with sub-cortical dementia. These white matter lesions were suggested by Bearden et al. (38) to play an increasing role in bipolar cognitive impairment with age, perhaps explaining the associations between number of episodes of illness and neuropsychological task performance (see below), and providing evidence in favour of position (iii) (the degenerative lesion hypothesis). The problem with this hypothesis is that it is only a minority of bipolar patients that actually present with WMH. Bearden et al. (38) calculated a moderate overall effect size of about 0.28, which while statistically significant, cannot account for the weight of cognitive dysfunction in bipolar disorder. Secondly, the effect of WMH on cognition is in the authors' opinion still unresolved. In contrast to the data collected by Bearden et al. (38), Krabbendam et al. (18) attempted to relate the cognitive functioning of bipolar patients to the presence of WMH and found no differences in cognitive performance between patients with and without these lesions.

The collection of statistically significant findings from the imaging literature have also not yielded corresponding excitement in the neuropathology field. As Harrison noted in his review of post-mortem studies of bipolar disorder, 'a conventional neurodegenerative process is unlikely to underlie mood disorder…' (20, p. 1441). The most salient findings according to Harrison (20) are decreased glial cell density of the subgenual (101, 102) and dorsolateral prefrontal cortex (103, 104). Even these changes, however, have to be interpreted in the light of many of the same methodological problems that confound the neuropsychological data. There tends to be a selection bias in favour of suicide victims, and the long-term effect of

medication and alcohol may cause pathological changes that are erroneously attributed to affective symptomatology (20, 105).

Weinberger and McClure (106), writing in the context of the schizophrenias, have cautioned against interpreting *in vivo* MRI findings of grey matter loss as evidence for progressive structural neurodegeneration. Not only have post-mortem studies failed to provide consistent evidence of neuronal loss or gliosis, but there is a conspicuous absence of increased expression of genes involved in cellular response to injury (106). Similar negative findings characterize the bipolar disorder literature (20, 107, 108). As pointed out by Bradshaw and Sheppard (77), the at least partially successful treatment of mood disorders with medication favours a neurochemical as opposed to a degenerative structural aetiology. The imaging data which purport to show progressive degeneration may instead reflect differences in imaging techniques, physiological alterations in tissue such as water content, changes in body weight, alcohol intake and hormone levels, and medication use (106).

There is direct evidence for this view. Dendritic spine density changes in the dentate gyrus and CA1 regions of the hippocampus have been demonstrated in animal models after administration of selective serotonin reuptake inhibitors and tricyclic antidepressants (109). Smaller hippocampal volumes observed in patients with Cushing's disease have been shown to return to normal after treatment (110, 111). Drevets et al. (61) found no grey matter volume differences between lithium-treated bipolar and control groups. The group of patients with bipolar disorder who did not receive lithium, however, displayed a significant reduction in cortical volume compared with the treated patients and controls (61). The lithium-associated morphological changes most likely reflect a recovery of the integrity of neuronal axons and dendrites (109). Similar morphological changes have been reported in other brain regions. Paroxetine has been hypothesized to cause a decrease in thalamic volumes (112) and neuroleptic medications have been implicated in striatal (113, 114), and frontal lobe volume changes (115, 116).

If a gross structural pathology underpins bipolar disorder, its nature remains opaque. A neurodegenerative process is equally unfavoured by the neuropathological or structural imaging data. Nevertheless, a large number of studies have reported associations between cognitive performance and duration or number of affective episodes, and this appears at first glance to contradict the imaging and pathology evidence discussed above.

The association between task performance and number of affective episodes

Neuropsychological deficits have been shown to correlate with both the number of affective episodes and the overall duration of illness (5, 11, 12, 24, 117, 118). Similar associations between illness episodes and the volume of various cerebral structures are commonly reported (92, 119, 120). Sixteen of the 21 studies listed in Table 2 report an association between the number of manic or depressive episodes experienced and neurocognitive function. Performance on memory and 'executive' tasks were most likely to correlate with illness episodes.

McKay et al. (56) carried out a three-way comparison of young, elderly, and chronic patients with bipolar disorder. A greater number of chronic patients scored in the severely impaired range on a memory and executive battery than their counterparts with fewer past episodes. Kessing (17) reported that patients with two or more illness episodes performed significantly worse than patients with just one episode on the Cambridge Cognitive Examination and the Mattis Dementia Rating Scale. Similarly, Strakowski et al. (92) compared the ventricular and periventricular volumes of first-episode bipolar patients to subjects with multiple affective episodes as well as healthy controls using MRI. Patients with a history of multiple episodes displayed significantly larger lateral ventricles than the single-episode bipolar group supposedly indicating a progressive loss of tissue over the course of the disorder (92). The episode–task performance association has been replicated in other cohorts with a variety of different psychometric instruments (9, 13, although see 4, 25, 121, 122 for a divergent opinion).

In addition, an intriguing relationship between dementia and unipolar and bipolar depression has been detailed (123). The authors examined a cohort of close to 14 000 people hospitalized with a mood disorder, 81 380 patients with osteoarthritis and 69 149 patients with diabetes. The risk of receiving a diagnosis of dementia on subsequent readmission was elevated in the affective disorder group compared with the two control groups (123).

Although these data appear to suggest the presence of a structural neurodegenerative process, there are alternative explanations. Patients who are more severely affected are likely to experience a greater number of affective episodes, and a greater number of hospitalizations than their counterparts with a more benign form of the illness. They are also likely to be treated with higher doses and greater combinations of medication (124) and

Table 2. Relationship between number of affective episodes and neuropsychological task performance in individuals with bipolar affective disorder

Study	Sample size	Nature of the association
Martinez-Aran et al. (59)	108 BP (various) + 30 controls	No. of hospitalizations + no. of manic episodes associated with learning and memory performance
Fossati et al. (205)	23 FE depressives + 28 unipolar recurrent + 88 controls	Recurrent unipolar subjects displayed impaired verbal recall compared to FE patients
Donaldson et al. (26)	43 bipolar I patients	History of psychosis and duration of illness associated with general but not working memory score on WMS
Naismith et al. (51)	55 UP + 22 controls	No association between no. or duration of depressive episodes + 'executive' neuropsychological tasks
Clark et al. (5)	30 patients with bipolar disorder + 30 controls	Performance on the CVLT + RVIP influenced by no. of manic + depressive episodes. TOL + SWM only affected by no. of depressive episodes
Cavanagh et al. (11)	20 patients with bipolar disorder + 20 controls	Performance on the CVLT affected by previous no. of manic episodes
Lebowitz et al. (12)	45 manic inpatients + 30 controls	Verbal fluency deficits associated with no. of manic episodes
El-Badri et al. (118)	29 euthymic bipolar individuals + 26 controls	No. of 'affective' episodes associated with TMT-B, DMTS + TOL performance
Zubieta et al. (24)	15 euthymic bipolar individuals + 15 controls	No. of manic, depressive episodes, and hospitalizations for mania associated with WCST performance
Swann et al. (191)	28 euthymic bipolar patients + 28 controls	No. of depressive episodes affected performance on the VBM task
Rubinsztein et al. (84)	18 bipolar subjects in remission	Scores on the DMTS test correlated with the total no. of months hospitalized
Scott et al. (86)	41 euthymic bipolars + 20 controls	No. of episodes correlated with problem solving as evinced by the MEPS
Verdoux and Liraud (122)	33 bipolar inpatients	No significant associations between neuropsychological performance and duration of illness
Ferrier et al. (4)	21 good, 20 poor outcome bipolar patients + 20 controls	No significant relationship between outcome[a] and test performance
Denicoff et al. (117)	49 relatively euthymic patients	No. of manic and depressive episodes correlated with performance on WCST. No. of hospitalizations for mania associated with VCT + WCST performance. No. of hospitalizations for depression associated with CVLT performance
van Gorp et al. (9)	25 euthymic bipolars + 22 controls	Performance on CVLT, WCST, Stroop and TMT-B associated with total no. of months manic and no. of months depressed
Atre-Viadya et al. (25)	36 euthymic bipolars	Duration of illness had no significant effect on cognitive performance
Kessing (17)	28 bipolar patients + 58 controls	No. of depressive episodes correlated with cognitive decline as measured by the CAMCOG + MDRS
Tham et al. (13)	26 euthymic bipolar patients	No. of hospitalizations (for both mania + depression) associated with performance on SRB and TMT (A + B). TMT-A performance associated with length of illness
McKay et al. (56)	45 mixed UP and BP (24 young, 21 elderly/chronic)	Cognitive impairment associated with chronic illness only
Hoff et al. (121)	35 manic inpatients	Duration of illness not correlated with performance on cognitive tasks. However, no. of previous hospitalizations inversely correlated with right-hand performance on PPT

BP = bipolar disorder; CAMCOG = Cambridge Cognitive Examination; CVLT = California Verbal Learning Test; DMTS = Delayed Matching to Sample; FE = First Episode; LDST = Letter Digit Substitution Task; MDRS = Mattis Dementia Rating Scale; MEPS = Means-Ends Problem-Solving; PPT = Purdue Pegboard Test; RVIP = Rapid Visual Information Processing; SRB = Synonym, Reasoning and Block Test Battery; SWM = Spatial Working Memory; TMT-A = Trail Making Test Part A; TMT-B = Trail Making Test Part B; TOL = Tower of London; UP = unipolar depression; VBM = Visual Backward Masking Task; VCT = Visual Cancellation Task; WCST = Wisconsin Card Sorting Test; WMS = Wechsler Memory Scale.

[a]Outcome was defined as the frequency, duration and severity of affective episodes and their psychosocial sequelae (4).

electroconvulsive therapy (ECT). Pizzagalli et al. (62) made the point that abnormalities of the subgenual prefrontal cortex have been reported in severely depressed and hospitalized samples of patients, but not in less ill or unmedicated bipolar cohorts. Cognitive deficits, especially psychomotor retardation, are more pronounced in melancholic than non-melancholic depression (125). Albus et al. (126) hypothesized that neuropsychological dysfunction is a product of psychosis, rather then affective illness *per se*, a hypothesis partially confirmed by other researchers (24, 7). Kato et al. (127) reported that patients with psychotic features displayed greater ventricular enlargement than their non-psychotic counterparts.

Secondly, patients who have experienced multiple episodes of illness tend to experience a truncation of the mood 'cycle' over time, with numerous spontaneous affective episodes, and less symptom-free periods (128). Thus the possibility is raised that instead of reflecting long-term damage to the brain, poor cognitive performance in multi-episode patients may be indicative of the presence of chronic affective symptomatology. Coryell et al. (129) concluded that bipolar disorder results in profound psychosocial impairment that persists for years even in cases where resolution of the acute clinical symptoms has occurred. Weinberger and McClure (106) hypothesized that psychosocial impairment such as long-term unemployment may also lead to detectable plastic alterations of neuronal connections without necessarily being indicative of an irreversible neurodegenerative process.

The higher incidence of dementia in patients with affective disorders may be due to the fact that acute depression can be misclassified as dementia when cognitive dysfunction is a dominant symptom (123). Confounding factors such as alcoholism and drug abuse are also likely to be higher in the bipolar and depressed groups although these factors were putatively controlled for by the authors in question. Even if a causal relationship between the affective disorders and dementia exists, only a small minority of patients actually presented with dementia and thus a degenerative process cannot account for the cognitive dysfunction in the vast majority of bipolar individuals.

In summary then, position (ii) – the adverse effects of mood state on cognition – has not been entirely ruled out as a contributing factor to bipolar cognitive dysfunction. Nevertheless, positions (iii)–(v) – that is enduring structural or functional neural changes leading to cognitive dysfunction – appear to be stronger hypotheses. The pathology and imaging literature has however failed to unequivocally identify regions of structural brain damage, and this together with the observation that cognition illness duration correlates do not prove the existence of a degenerative process, lead us to favour position (v). In the following sections we outline some of the preliminary imaging data describing state-independent changes in depression, and then discuss the evidence that these putative functional changes to parts of the brain involved in cognition or emotion have a neurodevelopmental or genetic origin.

The neurophysiological correlates of enduring functional deficits

Strakowski et al. (130) noted that the dearth of functional imaging studies of euthymic patients with bipolar disorder makes it difficult to draw conclusions about any underlying trait abnormality. Nevertheless, they speculated that the neural networks subserving emotion appear to be over-reactive leading to compensatory over-activation of cortical regions to allow cognitive tasks to be discharged. Strakowski et al. (131) detected over-activity of the ventrolateral prefrontal cortex, parahippocampal gyrus and amygdala but other studies have suggested under-activation of the ventral prefrontal cortex (67), increased cerebellar metabolism (132), and a pattern of frontal hemispheric asymmetry with lower activity of the left anterior cingulate and prefrontal cortex (74) to be a signature of a bipolar diathesis.

The data are thus too preliminary to conclusively identify the neural correlates of the functional disturbance that is hypothesized to lead to bipolar disorder. Nevertheless, it is likely that more subtle abnormalities of the same neural circuit (the fronto-striatal-thalamic loop) involved in acute mood shifts and their amelioration through treatment may constitute trait markers for bipolar affective illness. Dense iterative and reciprocal connections between limbic structures and the prefrontal cortex and striatum (78, 130, 133) may explain the dysregulation of emotional control and concomitant dysfunction of executive cognitive processes that an abnormality in this circuit will precipitate.

Evidence for neurocognitive dysfunction as a premorbid, congenital trait

Evidence suggests that the observed neurocognitive deficits in individuals with bipolar disorder are not merely the product of affective symptomatology or medication use, but are reflective of pre-morbid developmental abnormalities. Support for this

theoretical position is derived from a variety of methodological approaches: twin studies, comparisons of cases with positive and negative family histories, retrospective analyses of premorbid function, and assessment of unaffected biological relatives.

Twin studies allow for the analysis of genetic effects against a homogenous environmental background, and thus cognitive differences in discordant twin pairs can be attributed to the effects of affective illness. Gourovitch et al. (134) compared the neuropsychological performance of monozygotic twins discordant for bipolar disorder and found memory deficits – as evinced by the Wechsler Memory Scale (WMS) and the California Verbal Learning Test – in the both the non-affected and affected members of the twin pair. The affected twins did however display a more pervasive pattern of memory deficits than their unaffected siblings: they showed recognition as well as recall difficulties while their healthy counterparts displayed only recall problems (134).

There are alternative explanations for the Gourovitch et al. (134) finding. Four of seven of the twin pairs were depressed or manic during testing, and thus the discrepancy in cognitive functioning between the ill and well twins is confounded by mood. The data could also have been distorted by the presence of residual symptoms in the unaffected twins even if formal DSM-IV criteria were not met (see below).

The appearance of putative neuropsychological deficits in the unaffected twin extends to 'structural' abnormalities of neural tissue as evinced by MRI. Noga et al. (135) contrasted six monozygotic twin pairs discordant for bipolar disorder with a control group of unaffected twins, and found that the right hippocampus was smaller in the sick bipolar twins, but that both ill and well twins had larger caudate nuclei than their control counterparts, implicating the latter structure as a genetic risk factor for the development of manic depressive illness. In a similar study of a Finnish twin cohort, both affected and unaffected twins displayed decreased left hemispheric white matter volumes compared with control twin subjects (136).

The role of genetic factors is also alluded to by Tabares-Seisdedos et al. (137) who argue that patients with bipolar disorder who have a positive family history of psychosis perform worse on tests of visual-motor processing and attention than sporadic cases of the disorder. Hirayasu et al. (138) reported that the left subgenual cingulate of first episode affective disorder patients with a family history of illness was 20–24% smaller than in patients with no family history of affective illness and healthy controls.

A number of retrospective case–control studies suggest that affective disorders may have neurodevelopmental antecedents. Crow et al. (139) found that adults presenting with affective psychosis displayed an excess of premorbid motor and intellectual deficits compared with controls from the same birth cohort. van Os et al. (140) observed that children with affective disorders were delayed in reaching motor development milestones, and suffered from twice as many speech abnormalities as their peers. More recently, Sigurdsson et al. (141) reported an increased prevalence of retarded language, social and motor development in a group of adolescents with bipolar disorder or depressive psychosis. In a prospective study, Hellgren et al. (142) followed 56 Swedish adolescents who evinced developmental deficits at the age of 6 years, and observed an increased rate of psychiatric disorder (especially major depression) relative to controls from the same cohort. Seven percent of the developmental delay group went on to develop bipolar disorder, compared with 0% of the control group (142).

Keri et al. (143) showed that the unaffected relatives of their bipolar group displayed a greater degree of verbal recall difficulties than a group of unrelated controls. Interestingly, this finding has been replicated by Chowdhury et al. (144) who argue for a trait deficit in the executive control of working memory. Zalla et al. (145) reported that bipolar patients and their unaffected relatives performed poorly on the Stroop test, a result the authors attribute to dysfunction of the anterior cingulate cortex. Kestenbaum (146) and Decina et al. (147) examined the high-risk offspring of bipolar parents and asserted that a significantly higher verbal than performance IQ may be a signature of genetic susceptibility. These results are congruent with Flor-Henry et al.'s (148) hypothesis of right hemisphere dysfunction and reversed lateral dominance in mania, although Bearden et al. (38) asserted that the verbal performance dichotomy is small and therefore unlikely to be of clinical significance.

Ahearn et al. (149) examined 21 members of a pedigree with a high genetic loading for bipolar disorder with MRI and reported white matter and sub-cortical grey matter lesions in a number of affected and unaffected family members, suggesting that these changes may represent biological markers for the illness. Pierson et al. (150) uncovered p300 ERP abnormalities in the non-affected relatives of bipolar patients. A lack of p300 amplitude dominance in the right hemisphere was observed in

the relatives compared with the control group. DelBello et al. (151) reported an increase in hippocampal size in bipolar offspring who presented with affective symptomatology but did not meet the DSM-IV criteria for bipolar disorder.

A weakness inherent in studies of at-risk relatives is the higher rate of psychopathology, and greater exposure to significant environmental stressors in the at-risk groups (152, 153). Even if the relatives do not meet the criteria for bipolar disorder, they may suffer from prodromal symptoms or present with other psychopathology that causes neurocognitive dysfunction. It is possible, however, that the genes that predispose to bipolar disorder have pleiotropic effects and increase the risk of developing a range of psychopathology as well as cognitive deficits, ameliorating this methodological concern. Psychotic illnesses have been shown to have a lengthy prodromal period (154), and symptoms of depression, hyperactivity, and hypomania are often present before the age of 15 even if no diagnosis has been made (155).

In one study that has at least partially controlled for these difficulties, however, it was discovered that 8–12-year-old children who had at least one parent with bipolar disorder performed worse on executive and non-verbal intelligence test-associated tasks than a matched group of children with healthy parents (156). The finding still held when the children with subsyndromal mood symptoms were excluded from the statistical analysis.

Not all studies of 'at-risk' relatives or premorbid bipolar individuals have however, reported the presence of cognitive deficits. Kremen et al. (157) reported a wide range of cognitive deficits in the relatives of schizophrenics, but not bipolar disorder. Gilvarry et al. (158) were unable to detect significant neuropsychological deficits in the biological relatives of manic depressive individuals. McNeil and Schubert (159) also found neuropsychological deficits in the unaffected offspring of schizophrenics, but not in the offspring of bipolar probands.

Quackenbush et al. (160) analysed the premorbid academic functioning of a cohort of adolescent bipolars and argued that 85% of the sample demonstrated 'good to excellent' premorbid academic achievement. Interestingly, 39% of the sample had difficulties with mathematics, although it is unclear how this compares with the rest of the population. Lagace et al. (161), however, replicated this observation in remitted adolescent bipolar patients. In a similar vein, Kutcher et al. (162) conducted a retrospective evaluation of the premorbid functioning of 28 adolescents with bipolar disorder by reviewing their school records, and reported that approximately 67% of the sample evinced good to excellent academic achievement prior to their illness. These data are supported by more recent studies (163, 164) finding that a premorbid group of non-psychotic bipolar patients did not differ from unaffected controls on any measure of intellectual functioning; and that neither mania nor depression was associated with childhood dysfunction. A cohort of 60 bipolar offspring was reported to demonstrate a good level of functioning as evinced by the Global Assessment of Functioning (76 ± 12), and the Wide Range Achievement Test, a measure of academic performance (165).

Genetic factors influencing neuropsychological task performance

In the authors' opinion the weight of evidence suggests that the cognitive and imaging abnormalities of the first-degree bipolar relatives discussed above constitute genetic trait markers or endophenotypes for the illness, although sub-threshold fluctuations in mood remain a methodological problem. The following molecular genetic data support this conclusion.

Weinberger's group has been at the forefront of assessing the effects of genetic polymorphisms on neurocognitive function. Egan et al. (166) demonstrated that a functional single nucleotide polymorphism (SNP) that results in a valine to methionine amino acid substitution at codon 66 (val66met) of the brain-derived neurotrophic growth factor protein, influences human memory and hippocampal function. The valine allele was associated with poorer memory performance as evinced by the WMS, abnormal hippocampal activation on functional magnetic resonance imaging (fMRI), and lower hippocampal *N*-acetyl aspartate (NAA) as assayed by MRI spectroscopy (166). Another functional SNP in the catechol-*o*-methyltransferase (COMT) gene that results in a methionine–valine substitution, has been shown to affect prefrontal function and performance on the WCST (167). Hariri et al. (168) demonstrated that a serotonin transporter gene (SERT) polymorphism is associated not only with greater levels of fear and anxiety, but also with greater fMRI-illustrated activity in the amygdala.

Variants of genes such as SERT, COMT and BDNF are not only associated with cognitive functions, but have also been demonstrated to be over-represented in samples of individuals with bipolar affective disorder (169–173). Bearing in mind the caveat that for a variety of methodological reasons, genetic association studies are

susceptible to false-positive results (173–175) these data suggest some causal link between genetic variants that influence cognitive processes and a bipolar disorder diathesis.

The difficulty for proponents of this position is to reconcile this picture of cognitive deficits with the evidence for outstanding intellectual and creative achievements in individuals with bipolar disorder and their genetic relatives (176). For instance there is a well-known association between creative accomplishment in the arts and affective illness (177, 178), and a similar relationship has been reported in science and politics (179, 180). Goodwin and Jamison (181) have extended this observation to general intelligence – as measured by IQ scores – and are intermittently supported by the literature. Gilvarry et al. (158) observed higher IQ scores as evinced by the National Adult Reading Test in the unaffected first-degree relatives of bipolar individuals compared with controls, while Donaldson et al. (26) found that patients with a family history of bipolar disorder scored on average 11.7 points higher on IQ tests than sporadically ill individuals.

One response is to argue that creativity and intelligence are independent mental abilities and enhanced creativity is the product of the fluent, rapid and over-inclusive thinking associated with mania or hypomania rather than an intrinsic trait (177, 178). The IQ score data are not however amenable to this interpretation. Perhaps differences in cognitive test scores should not be pathologized. It is unlikely from an evolutionary point of view for genetic variants which produce generalized cognitive deficits to be maintained at such high frequencies in the population. A more plausible alternative is that the polymorphisms under discussion offer differential advantages under disparate environmental conditions. That is, we concur with Bradshaw and Sheppard (77) who drew a parallel between a balanced polymorphism model (182) of which heterozygote advantage in sickle cell anaemia is the prototypical example, and phenotypic variation in 'executive' performance.

There is already some tacit evidence from the schizophrenia literature supporting this position. A reviewer of this paper drew our attention to the work of Isohanni et al. (183) who described a cohort of schizophrenics with outstanding school performance despite the fact that there is a well-known association between schizophrenia and poor academic performance. Isohanni et al. (183) speculated that it is the degree of deviation rather than the direction of deviation from the norm that increases the risk for schizophrenia. Perhaps the 'bipolar genotype' also predisposes the individual to deviate from the norm, and environmental conditions determine the direction of this divergence. Tsuchiya et al. (184) examined 947 cases of bipolar disorder hospitalized between 1981 and 1998 and 47 350 matched controls. It was found that the bipolar patients had a shorter education history and a lower income than the control group. Their parents, however, had more years of higher education and were wealthier than the controls (184).

Neuropsychological dysfunction as a potential endophenotype for molecular genetic studies

A recent review discussing the feasibility of neuropsychological endophenotypes in genetic studies of bipolar disorder concluded that executive dysfunction and declarative memory disturbances are neurocognitive traits that may be markers of a bipolar diathesis (185). This proposal is largely congruent with the data presented here. One point of departure is the interpretation of these hypothesized declarative memory deficits. While Glahn et al. (185) suggested that verbal memory dysfunction may be a marker of either frontal or temporal lobe dysfunction, we suggest that in the absence of any evidence for an axial memory disorder, dysfunction of the fronto-striatal network is a more plausible possibility.

Functional disturbance and the structural tradition in neuropsychology

Is our disavowal of the notion of permanent structural lesions in bipolar disorder reconcilable with the above evidence cited by us, putatively indicating structural changes (endophenotypes) in the relatives of bipolar probands? We do not challenge the fact that MRI deviations can be detected in bipolar patients or their relatives. At issue is here the interpretation of what these anomalies represent on a neurophysiological level. As discussed on pages 222 and 223, volumetric changes as evinced by MRI cannot necessarily be equated with permanent, degenerative structural lesions. From a purely philosophical point of view the distinction between functional and structural changes is in any case arbitrary. When do functional changes become structural? Is an abnormal upregulation of receptors, for example, a functional or a structural anomaly?

Nevertheless, we believe that despite its fuzzy boundaries, the division between structural and functional effects is critically important to the way in which a disorder is conceptualized and therefore

the manner in which neuropsychological data are interpreted. Our conclusion that enduring functional changes to key neural networks lead to the emotional and cognitive disturbance associated with bipolar disorder has important theoretical and clinical implications for neuropsychology and neuropsychiatry.

As Liotti and Mayberg (76) pointed out, our knowledge of anatomical-cognitive function relationships is *in statu nascendi*. Most existing knowledge is derived from lesion studies where localization of function is the traditional paradigm. This tradition prompted Jackson (186), long ago, to caution that the localization of a lesion is not synonymous with the localization of a function. The true, dynamic complexity of the neural underpinning of mental life is only now fully revealing itself with the advent of *in vivo* functional imaging techniques. This complexity is perhaps best illustrated by the limited overlap between the traditional 'centred' for specific cognitive function derived from lesion data and the distributed field of activation identified by functional brain imaging of the same cognitive function. Yet neuropsychological data derived from psychometric assessment of psychiatric patients are often interpreted as though the purpose of the exercise is to localize a lesion (perhaps because of an explicit or implicit notion of structural pathology in bipolar disorder). This involves extrapolation from one body of knowledge (clinical–anatomical correlation) to another (functional neurodynamic), which may well lead to misleading conclusions.

We therefore argue that it may be inaccurate on the basis of neuropsychological testing to label psychiatric patients as suffering from specific anatomical impairments as these focal implications do not necessarily follow unless or until they have been separately demonstrated. The best imaging evidence available today implicates dynamically interrelated fronto-striatal systems in depressive or manic states and activation or deactivation of these systems appears to correlate diffusely with level of performance on 'executive' type measures (47, 65, 68, 75, 187–189). Nevertheless, to label people with bipolar disorder as suffering from a focal, neuropsychological 'dysexecutive' syndrome is probably over-simplistic because it equates functional (and most likely) genetically driven variation in highly dynamical and interdependent networks supporting various aspects of cognition and affect with a syndrome that normally occurs when a specific component or components of these networks are focally lesioned in stroke, head injury and tumour. The consequences of a distributed neurodynamic anomaly are surely likely to differ fundamentally from those of anatomically focal structural damage.

Conclusion

It is our contention that bipolar and other affective disorders are not caused by permanent structural lesions to the brain, and that a degenerative process is unlikely. Nevertheless, the presence of a small dementing minority cannot be ruled out on the basis of current data. The emotional and cognitive abnormalities of the illness may rather be the product of durable functional alterations of dynamic neural networks involved in mood and cognition. This functional disturbance appears to have a neurodevelopmental, possibly genetic aetiology. We note however, that plastic changes associated with a mood-driven disturbance of attention may adversely affect cognition particularly in the acute stages of the illness. If our aetiological speculation is correct then analysis of 'executive'-type cognitive traits may constitute a key endophenotype (vulnerability marker) for genetic studies of bipolar disorder.

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