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Impaired implicit sequence learning in depression: a probe for frontostriatal dysfunction?

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ABSTRACT

Background. Implicit learning through motor sequencing tasks is sensitive to basal ganglia dysfunction. Consequently, it is ideally suited for testing elements of the frontostriatal model of major depression and performance can be related to key clinical, neuropsychological, vascular and biochemical data.

Method. Twenty-one subjects with moderate to severe unipolar depression and 21 age-, sex- and education-matched controls were recruited. Clinical, vascular and biochemical data were recorded. Subjects were administered a battery of neuropsychological tests that assessed speed of processing, working memory, learning, memory, language, perceptual organization and executive functioning. Additionally, subjects were administered a motor sequencing implicit learning task. Implicit learning is assumed when reaction times improve during the sequenced condition as compared to the pseudo-random baseline condition.

Results. The rate of implicit learning in persons with depression was only half that of control subjects (3·6% *v.* 7·3%). Lower rates of implicit learning in patients were associated with poorer performance on neuropsychological tests of visuomotor speed and mental flexibility, longer duration of depressive episode and severity of acute stress. In a small number of subjects, poorer performance was also related to past suicide attempt.

Conclusions. Impaired implicit learning in persons with depression is consistent with frontostriatal dysfunction. Performance is related to some clinical characteristics and to neuropsychological functioning on tests of visuomotor speed and mental flexibility.

INTRODUCTION

A convergence of evidence over the past two decades suggests that disruptions of fronto-subcortical circuitry underpin the key symptoms of major depression. Neuroimaging has shown various abnormalities in these circuits including reduced perfusion in frontal, temporal and striatal regions (Mayberg *et al.* 1994; Elliott *et al.* 1997; Hickie *et al.* 1999), increased rates of white matter change (Hickie *et al.* 1995, 1997) and decreased volumes of the frontal cortex (Coffey *et al.* 1993), the hippocampus (Hickie *et al.* 2005*a*) and striatum (Husain *et al.* 1991; Krishnan *et al.* 1992). The striatum has been of particular interest because of its role in psychomotor retardation, a common feature of depression (Hickie, 1996; Naismith *et al.* 2002). In addition, as the striatum is often affected by small vessel disease, lesions in this area and the surrounding white matter may disrupt frontostriatal circuitry and underpin depression of later onset, giving rise to 'vascular depression' (Hickie & Scott, 1998). Thus, vascular risk factors (e.g. cholesterol, heart disease, smoking history, diabetes, hypertension and family

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history) in middle-aged or older persons have been increasingly examined as they are amenable to preventative treatment techniques. Levels of vitamin B12, folate and the sulfur-containing amino acid homocysteine are also being increasingly linked to vascular health, cognitive impairment and depression (Reynolds, 2002; Hickie *et al.* 2005*b*). Accordingly, there is a need to incorporate information pertaining to vascular health and homocysteine metabolism when examining frontosubcortical circuits in depression (Naismith *et al.* 2002; Hickie *et al.* 2005*a*, *b*).

Neuropsychological studies in depression have shown dysfunction across a range of domains including attention, learning, memory, processing speed and executive functioning. The most pronounced deficits are in the areas of psychomotor speed and mental flexibility (Veiel, 1997; Naismith *et al.* 2003), also supporting frontostriatal dysfunction. However, deficits vary according to the presenting clinical picture and complex aetiological pathways (Hickie, 1996; Naismith *et al.* 2003). It has also been suggested that attentional (Cassens *et al.* 1990) and motivational (Mialet *et al.* 1996; Elliott, 1998) factors influence results, with degree of task effort and complex attentive search strategies likely to impede performance (Thomas *et al.* 1999; Hammar *et al.* 2003).

To ascertain whether cognitive functioning improves as a consequence of attention to task demands, performance can alternatively be examined and compared through implicit learning (IL). IL is demonstrated through improvements in performance without conscious awareness of learned patterns (Schacter & Curran, 2000). Implicit sequence learning by serial reaction time tasks (i.e. motor sequencing) is generally regarded as being sensitive to frontal and subcortical impairment, with a specific role of the striatum being well established (Rauch *et al.* 1995, 1997*a*, 1998; Aizenstein *et al.* 2002; Exner *et al.* 2002). Although influenced by age (Curran, 1997), IL is generally intact in healthy elderly individuals (Howard & Howard, 1992) and in patient groups (e.g. animal phobias), where the basal ganglia are not thought to be involved in pathophysiology (Martis *et al.* 2004). IL is, however, decreased in those with disorders of basal ganglia circuits such as Parkinson's disease (Jackson *et al.* 1995), Huntington's disease (Knopman & Nissen, 1991) and obsessive compulsive disorder (Rauch *et al.* 1995, 1997*b*). These findings suggest that such tasks are useful 'probes' of basal ganglia function and may be ideally suited for testing the frontosubcortical model of depression, particularly in combination with functional neuroimaging.

In depression, no known studies have examined IL through motor sequencing tests, and examination of IL by other cognitive tasks (i.e. word-stem, priming, mood-congruent biases) has yielded inconsistent results (e.g. Bazin *et al.* 1994; Banos *et al.* 2001; Tarsia *et al.* 2003). The primary aim of this study was to examine the clinical utility and appropriateness of a previously established IL motor sequencing task (Rauch *et al.* 1995, 1997*a*, 1998) and to determine the relationship of IL with clinical, neuropsychological, vascular, biochemical and genetic data in persons with depression. It was hypothesized that patients with unipolar depression would have impaired IL and that performance would be correlated with domains primarily subserved by subcortical circuits (i.e. psychomotor speed), rather than those subserved by other regions such as the medial temporal lobe (i.e. explicit memory).

METHOD

Subjects

A previously unreported sample of patients with unipolar depression was recruited from specialist referral centres in south-eastern Sydney. Twenty-one age-, sex- and education-matched healthy volunteers screened for history of psychiatric illness were recruited from the community by newspaper advertisement. Exclusion criteria were: history of substance abuse or dependence; history of neurological disease or other illness known to affect cognitive functioning; electroconvulsive therapy within the past 3 months; visual and/or auditory impairments; history of head injury with loss of consciousness; major medical illness (e.g. cancer); poor English-speaking skills; and a Mini-mental State Examination (MMSE; Folstein *et al.* 1975) score less than 24 or diagnosis of dementia as determined by clinical and neuropsychological review. The study was approved by the institutional ethics committee and all subjects gave written informed consent.

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Medical assessment

Medical histories and details of vascular risk factors were recorded by self-report and interview. A cumulative vascular risk factor score (range 0–6) was calculated as reported previously (Hickie *et al.* 2001, 2005*a*, *b*; Naismith *et al.* 2002, 2003).

Psychiatric assessment

Patients underwent structured clinical assessment by a psychiatrist who completed the 17-item version of the Hamilton Depression Rating Scale (Hamilton-17; Hamilton, 1960), the CORE assessment tool for rating psychomotor dysfunction (Parker *et al.* 1994) and DSM-IV criteria (APA, 1994). Psychiatrists also rated the severity of acute and enduring stressors on a six-point scale (1–6): a score of 1 indicated no acute events or enduring circumstances that may be relevant to the disorder; a score of 6 indicated catastrophic acute or enduring stressors, such as the death of a relative or being held captive as a hostage respectively.

Biochemical testing

Blood samples were collected from each participant and serum B12 (pmol/l), serum folate (nmol/l), homocysteine (μmol/l) and total cholesterol (mmol/l) were measured.

Self-report

The 30-item Geriatric Depression Scale (GDS; Yesavage *et al.* 1982) was used to assess self-reported mood symptoms without a high somatic component (Naismith *et al.* 2004). State and trait anxiety were measured using Spielberger's State-Trait Anxiety Scale (Spielberger, 1983).

Neuropsychological assessment

In addition to the MMSE, a psychologist administered the following battery:

Pre-morbid intellect. The National Adult Reading Test (NART; Nelson & Willison, 1991) was used.

Information processing speed. A test of simple and choice reaction time was administered (Huppert, 1987; Naismith *et al.* 2003). Part A of the Trailmaking Test (TrailsA; Reitan, 1979) and the oral version of the Symbol Digit Modalities Test (Smith, 1982) were also used to assess motor and non-motor speed respectively.

Working memory. Subjects completed the Letter Number Sequencing subtest of the Wechsler Adult Intelligence Scale – 3rd edition (WAIS-III; Wechsler, 1997).

Learning. The Australian adaptation (Shores & Carstairs, 2000) of the Logical Memory subtest of the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987) was used (maximum = 50). Word-list learning was assessed by the Rey Auditory Verbal Learning Test (RAVLT; Lezak, 1995). Total learning over trials was used (RAVLTtot = summed trials 1 to 5, maximum = 75).

Memory. Delayed (30-min) recall scores for WMS-R Logical Memory were obtained and 'memory' was expressed according to percentage of material retained: (Logical Memory delay score/Logical Memory learning score) × 100. Similarly, percentage of words retained on the RAVLT was computed: (RAVLT delay/RAVLT learning trial 5) × 100. Scores greater than 100% were curtailed.

Language. Verbal fluency was assessed using phonetic (letters F, A, S) and semantic (animal names) strategies (Benton, 1967).

Perceptual organization. The WAIS-III (Wechsler, 1997) Picture Completion subtest was used as a measure of perceptual organization.

Executive functioning. The WAIS-III Matrix Reasoning subtest (Wechsler, 1997) was used as a test of non-verbal abstract reasoning and visual information processing without timed constraints.

To measure response inhibition and mental flexibility, often impaired in depression, the Stroop Test (Trenerry *et al.* 1989) and Part B of the Trailmaking Test (TrailsB; Reitan, 1979) were used respectively. As a test of planning, subjects also completed a computerized version of the Tower of London Test (Schall *et al.* 2003). Subjects were allowed 30 s to solve each problem, with results scored as either incorrect ('0')

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or correct ('1') (maximum score = 15). The 128-item computerized version of the Wisconsin Card Sorting Test (WCST; Heaton *et al.* 1993) was administered as a test of concept generation, set-shifting, response inhibition and general problem-solving abilities. All cards were administered and the total number of errors was recorded.

IL task

Subjects completed an IL task (see Fig. 1) as described by Rauch *et al.* (1995, 1997*a*). In a magnetic resonance scanner, subjects viewed images projected onto a screen by a mirror fitted to the head coil. The IL task was a serial reaction time task that entailed cued presentation at one of four positions corresponding to four keys on a response pad. Subjects used a separate finger for each key (the index and middle fingers of each hand).

The reaction time task included a programmed sequence within the otherwise pseudo-random order of stimulus presentation. This offered the possibility of IL of that programmed sequence, which would be reflected by an improvement in reaction time. Improved reaction time during the programmed sequence condition would imply IL, and was the variable of interest. Two alternating conditions were used, with stimuli occurring at a constant stimulus onset asynchrony (SOA) of 1·8 s: during the baseline (BL) condition, 24 stimuli appeared at pseudo-random locations, with the constraint that two consecutive stimuli did not appear in the same locations. In the IL condition, stimuli were presented in a fixed 12-item sequence (e.g. position 1 2 1 4 2 3 4 1 3 2 4 3) (see Fig. 1) repeated six times (a total of 72 stimuli). Three BL and four IL sequences were displayed in an alternating pattern for a total of 8 min 40 s (Run1). A second block using a different IL sequence was also run (Run2) and was counterbalanced across subjects.

Statistical analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 12. *t* tests, analysis of variance (ANOVA) and Mann–Whitney *U* tests were used according to distributions. Effect sizes were computed for neuropsychological data using Cohen's *d* (Cohen, 1988). Pearson and Spearman correlation coefficients were used where appropriate.

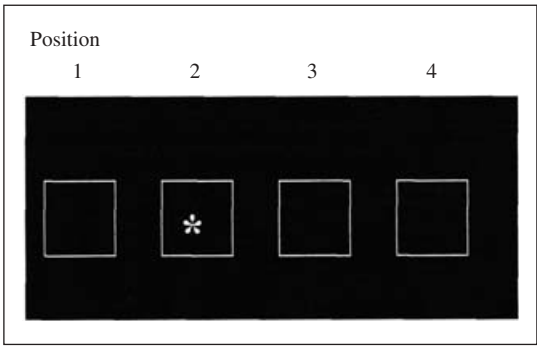

FIG. 1. Implicit learning serial reaction time task: screen display as viewed by the subject. The task requires the subject to respond to the target by pressing the corresponding button on the response pad. This figure indicates that a button response is required at position 2 (corresponding to the index finger of the left hand). Although the position of the target appears random, there is a sequence interspersed at blocked intervals. Improvement in reaction times during the sequenced condition reflects a reaction time advantage associated with implicit learning of that sequence.

RESULTS

Twenty-one patients with non-psychotic DSM-IV-defined major depression (mean age 53·9, range 25–77 years, S.D. = 11·8, 76% female) and 21 control subjects (mean age 50·8, range 25–69 years, S.D. = 11·7, 71% female) were recruited. Average depression severity, as measured by the Hamilton-17, was moderate (mean 21·7, range 13–32, S.D. = 4·4). Mean age of onset was 39·1 years (range 13–74, S.D. = 16·9). Six patients had late-onset (i.e. first onset after age 50) depression and/or melancholic depression. CORE scores ranged from 2 to 26 (mean score 8·8, S.D. = 7·2). None of the patients had psychotic features or bipolar disorder. The average number of lifetime episodes was 3·6 (S.D. = 3·3, maximum of 10). The duration of the current episode varied from 7 to 450 weeks (S.D. 140·0, maximum of 450 weeks). Duration of illness was calculated as 'current age minus age of depression onset' (Hickie *et al.* 2005*a*), and was on average 14·8 years (S.D. = 12·6). Mean severity of acute and enduring stressors was 3·2 (S.D. = 1·3) and 3·0 (S.D. = 1·1) respectively. Two patients were not receiving any antidepressant treatment. Two patients were being treated with

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Table 1. *Demographic, self-report, vascular and biochemical data for control subjects and persons with depression*

	Control mean (S.D.)	Depression mean (S.D.)	Test statistic	*p* value
Age, years[a]	50·8 (11·7)	53·9 (11·8)	0·7	0·398
Sex, % female[b]	71	76	0·1	0·726
Education, years[a]	13·2 (3·3)	12·9 (3·7)	0·1	0·758
Geriatric Depression Scale[c]	3·3 (2·5)	21·3 (8·2)	−4·8	0·000
State anxiety[c]	24·5 (3·9)	54·0 (14·6)	−5·2	0·000
Trait anxiety[c]	28·9 (6·1)	57·9 (13·5)	−4·9	0·000
Cumulative vascular risk, /6[a]	1·9 (1·4)	2·1 (1·4)	0·3	0·580
Homocysteine (μmol/l)[a]	10·1 (3·3)	10·8 (3·7)	0·5	0·499
Serum B12 (pmol/l)[a]	303·0 (140·6)	308·8 (136·6)	0·2	0·897
Serum folate (nmol/l)[a]	21·3 (10·6)	19·9 (10·0)	0·2	0·687
Cholesterol (mmol/l)[a]	5·3 (1·5)	5·6 (1·2)	0·6	0·452

[a] One-way analysis of variance; [b] χ^2 test; [c] Mann–Whitney *U* test.

older-generation tricyclic antidepressants. All others were being treated with newer-generation antidepressants, including one with monoamine oxidase inhibitors, eight with selective serotonin reuptake inhibitors, seven with serotonin and noradrenaline reuptake inhibitors and one with a noradrenergic and specific serotinergic antidepressant. One patient was receiving a low-dose atypical antipsychotic. Three patients were receiving lithium.

Group differences: control *versus* depressed subjects

There was no difference in age, sex, years of education or estimated pre-morbid intelligence (NART) between patients and control subjects (Table 1). As expected, patients had very high rates of state and trait anxiety and self-reported depression in the moderate to severe range (GDS). There was no difference between patients and control subjects in terms of cumulative vascular risk or levels of homocysteine, B12, folate or cholesterol.

Table 2 displays performance on neuropsychological tests and IL performance. Patients had significantly poorer performances than controls on the MMSE, and on most tests of motor and non-motor speed. They also had poorer performances on WAIS-III Picture Completion, and on TrailsB and the Stroop Test. There was no difference between patients and controls on tests of simple reaction time, WAIS-III Letter Number Sequencing, WMS-R Logical Memory, RAVLT (learning or memory retention), verbal fluency, Tower of London, WAIS-III Matrix Reasoning, or on the WCST.

Implicit learning task

Patient's reaction times were generally slower across BL and IL conditions for both Run1 and Run2 (Table 2). To take into account slowed BL reaction time and *degree* of reaction time advantage associated with the IL condition with the preservation of continuous data, a variable expressing percentage improvement in reaction time (PIRT) was computed:

$$\frac{\text{BL reaction time} - \text{IL reaction time}}{\text{BL reaction time}} \times 100.$$

This variable thus expressed degree of IL relative to BL. Using this variable, persons with depression showed significantly less percentage IL improvement on both Run1 and Run2 of the task, although this was particularly evident on Run2, where the IL task was associated with a 9% improvement in control subjects compared with only a 3% improvement in persons with depression.

For all remaining analyses relating IL with clinical, neuropsychological, vascular and biochemical data, however, percentage IL improvement was averaged over both Run1 and Run2 (PIRT) because, in practice, the effects of Run2 can only be observed following administration of Run1. The mean rate of improvement in control subjects using this measure was twice that of patients (7·3% *v.* 3·6%) and corresponded to a large effect size difference ($d = 0{\cdot}8$).

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Table 2. *Neuropsychological test scores and performance on the implicit learning task*

	Control mean (S.D.)	Depression mean (S.D.)	Effect size	Test statistic	*p* value
Neuropsychology					
Pre-morbid intellect[a]	115·5 (5·3)	111·7 (11·8)	0·4	3·0	0·091
MMSE[a]	29·6 (0·8)	28·1 (1·8)	1·1	−3·1	0·002
Simple reaction time[a#]	0·30 (0·05)	0·33 (0·09)	−0·4	2·9	0·098
Choice reaction time[b#]	0·66 (0·07)	0·77 (0·14)	−1·0	−2·9	0·004
Symbol Digit Modalities[b]	60·0 (8·0)	50·3 (15·0)	0·8	−3·5	0·000
TrailsA[a#]	30·5 (10·9)	39·1 (15·9)	−0·6	4·1	0·050
Let-Num Sequencing[a]	11·2 (2·2)	10·7 (2·6)	0·2	0·6	0·441
LogMemory, learning[a]	27·4 (6·8)	23·5 (6·1)	0·6	3·8	0·057
LogMem, % retention[a]	87·4 (9·6)	80·8 (13·5)	1·0	3·3	0·079
RAVLT total learning[a]	54·7 (10·0)	48·2 (11·4)	0·6	3·7	0·060
RAVLT, % retention[a]	83·3 (21·6)	78·0 (29·1)	0·2	0·5	0·508
Phonetic fluency[a]	40·7 (9·5)	34·8 (14·1)	0·5	2·5	0·120
Semantic fluency[a]	20·8 (4·1)	18·2 (5·1)	0·6	3·1	0·085
Picture Completion[b]	23·1 (1·8)	18·9 (4·7)	1·2	−3·6	0·000
Matrix Reasoning[a]	17·7 (5·6)	14·8 (6·0)	0·5	2·6	0·113
Stroop Test[a]	105·5 (12·6)	87·3 (21·6)	1·0	−2·6	0·008
TrailsB[b#]	62·8 (13·7)	90·8 (27·9)	−1·3	−3·2	0·001
Tower of London[a]	11·7 (1·6)	10·7 (2·0)	0·6	3·3	0·077
WCST, errors[a]	41·4 (19·4)	51·8 (20·3)	−0·5	2·8	0·105
Implicit learning task					
Run1-BL reaction time[a#]	0·51 (0·06)	0·58 (0·10)	−1·0	9·6	0·003
Run1-IL reaction time[a#]	0·47 (0·06)	0·56 (0·11)	−1·0	10·0	0·003
Run1 % improvement[a]	6·0 (5·4)	4·0 (4·3)	0·4	10·0	0·003
Run2-BL reaction time[a#]	0·49 (0·05)	0·59 (0·11)	−1·2	15·5	0·000
Run2-IL reaction time[a#]	0·44(0·07)	0·57 (0·12)	−1·3	17·6	0·000
Run2 % improvement[a]	8·6 (5·4)	3·1 (5·8)	1·0	10·0	0·003
Mean PIRT[a]	7·3 (4·7)	3·6 (4·5)	0·8	7·0	0·012

MMSE, Mini-mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; WCST, Wisconsin Card Sorting Test; BL, baseline; IL, implicit learning; PIRT, percentage improvement in reaction time across both Run1 and Run2.
[a] One-way analysis of variance; [b] Mann–Whitney *U* test *z* statistic; [#] measured in seconds.

IL performance: whole sample analyses

Relationship to demographic variables and self-reported depression and anxiety

There was no relationship between IL performance and age ($r=0{\cdot}03$, N.S.), sex ($t=-0{\cdot}1$, N.S.) or years of education ($r=0{\cdot}11$, N.S.). However, lower pre-morbid IQ was associated with lower rates of PIRT ($r=0{\cdot}37$, $p=0{\cdot}023$). Poorer PIRT was related to higher levels of self-reported depression ($r=-0{\cdot}35$, $p=0{\cdot}028$) and trait anxiety ($r=-0{\cdot}44$, $p=0{\cdot}004$) but only a trend association existed with state anxiety ($r=-0{\cdot}27$, $p=0{\cdot}093$).

Relationship to vascular and biochemical markers

For the whole sample, the relationship between PIRT and cumulative vascular risk ($r=0{\cdot}03$, N.S.) was non-significant ($t=0{\cdot}3$, N.S.). There was no relationship between PIRT and homocysteine ($r=0{\cdot}08$, N.S.), vitamin B12 ($r=-0{\cdot}12$, N.S.), folate ($r=0{\cdot}02$, N.S.) or cholesterol ($r=-0{\cdot}10$, N.S.) levels.

IL performance: persons with depression only

There was no relationship between PIRT and age ($r=0{\cdot}07$, N.S.), sex ($t=0{\cdot}6$, N.S.) or years of education ($r=0{\cdot}03$, N.S.). Table 3 displays data examining the relationship between PIRT scores and clinical and neuropsychological variables.

Relationship to clinical variables

There was no correlation between PIRT and severity of depression, clinician-rated psychomotor change, or age of depression onset, nor between melancholic *versus* non-melancholic ($t=0{\cdot}1$, N.S.) or early- *versus* late-onset ($t=-0{\cdot}5$, N.S.) subtypes. In patients only, the correlation between self-reported mood (GDS) and anxiety (state or trait) scores and PIRT was not significant.

Four patients had a history of suicide attempt. These patients had significantly lower

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Table 3. *Correlations between mean percentage improvement associated with the implicit learning task (PIRT) and key clinical and neuropsychological data*

	Pearson's *r*	*p* value
Hamilton-17 score[a]	−0·13	0·563
CORE score[b]	−0·23	0·322
Age of first depression onset	0·32	0·153
Geriatric Depression Scale	−0·01	0·951
State anxiety	−0·01	0·998
Trait anxiety	−0·26	0·254
Pre-morbid intellect	0·52	0·027
Mini-mental Status Examination	0·65	0·002
Symbol Digit Modalities Test (oral)	0·39	0·081
Choice reaction time	−0·40	0·078
TrailsA	−0·69	0·001
Picture completion	0·13	0·589
Stroop Test	0·27	0·232
TrailsB	−0·74	0·000

PIRT, percentage improvement in reaction time.
[a] Hamilton Depression Rating Scale, 17-item version.
[b] CORE scale for rating psychomotor retardation.

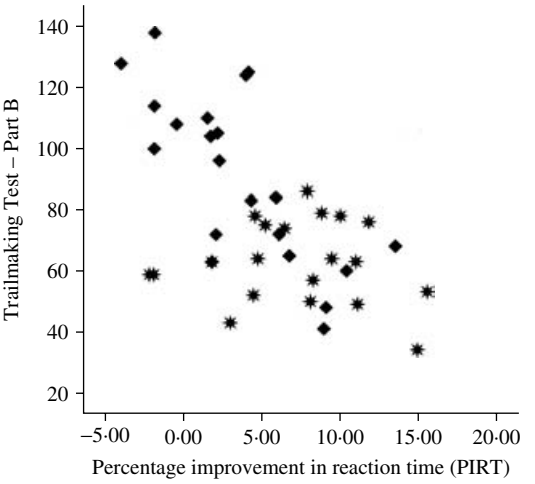

FIG. 2. Scatterplot of the association between performance on Part B of the Trailmaking Test and mean percentage improvement in reaction time (PIRT) on the implicit learning motor sequencing task for control subjects and patients with depression. Group: ✱, Control; ◆, Depression.

PIRT scores (no past attempt 4·3%, S.D. 4·0, past attempt −1·0%, S.D. 2·6, $t=2·5$, $p=0·024$). Although the association between PIRT and the number of lifetime depressive episodes was not significant ($r=-0·30$, N.S.), poorer PIRT was related to longer durations of current episode ($r=-0·53$, $p=0·013$). There was a trend for total number of years of illness to be related to poorer performance (Spearman's $r=-0·40$, $p=0·069$). There was also a trend for those subjects with a single episode (6·1%, S.D. 3·7) *versus* those with two or more episodes (2·5%, S.D. 4·4) to have better rates of PIRT ($t=-1·7$, $p=0·100$). There was no association between increasing severity of enduring stressors and PIRT ($r=-0·13$, N.S.). However, increasing severity of acute stressors was related to poorer PIRT ($r=-0·50$, $p=0·041$).

Relationship to neuropsychological variables

To reduce the number of statistical tests used, IL performance was only analysed with respect to those tasks in which persons with depression showed deficits relative to controls. As shown in Table 3, there was no association between lower PIRT and scores on the Stroop Test, WAIS-III Picture Completion, choice reaction time, or non-motor speed. However, PIRT was significantly correlated with higher pre-morbid IQ and better MMSE scores. PIRT was also correlated with the Trailmaking Test, even after controlling for age (TrailsA, partial $r=-0·70$, $p=0·001$; TrailsB, partial $r=-0·76$, $p<0·001$). The relationship between PIRT and TrailsB remained significant even after performance on TrailsA ($t=-2·7$, $p=0·014$, R^2 change = 15·3%) and pre-morbid IQ was statistically controlled for using stepwise regression ($t=-3·4$, $p=0·004$, R^2 change = 32·2%) (Fig. 2).

Relationship to vascular and biochemical markers

For patients, there was no relationship between PIRT and cumulative vascular risk ($r=-0·03$, N.S.). Although there was no relationship between PIRT and levels of homocysteine ($r=0·31$, N.S.), vitamin B12 ($r=0·08$, N.S.) or serum folate ($r=0·01$, N.S.), there was a trend association with cholesterol ($r=-0·44$, $p=0·060$).

DISCUSSION

This study is the first known to examine the relationship between implicit motor sequence learning and neuropsychological test performance in persons with depression. This is a theoretically driven paradigm designed to test the integrity of frontostriatal networks, which

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are thought to be intrinsic to the disorder. Additionally, as research in neuropsychiatry moves towards the integration of cognitive, clinical, vascular and biochemical data (Hickie, 1996), this study has allowed for the concurrent examination of a multitude of pathophysiologically relevant variables.

In general, across both control subjects and persons with depression, IL was unrelated to age, sex or years of education. It was also unrelated to vascular risk factors or to levels of homocysteine, folate, vitamin B12 or cholesterol. However, reduced learning was associated with higher self-reported levels of mood disturbance, higher trait anxiety and lower premorbid intellect. These findings indicate that the IL motor task is related to depressive and anxiety symptoms across a range of levels of symptom severity, and hence support its utility even in those with minor or subthreshold symptoms.

IL performance in persons with depression

As hypothesized, the participants of this study, who were out-patients with moderate to severe levels of unipolar depression, average to high average intellect and a reasonable level of education, had significantly lower rates of IL than age-, sex- and education-matched controls. These findings are consistent with prior research in basal ganglia disorders, and with theories implicating frontostriatal dysfunction in depression. While depressed patient's performance was pervasively slower, they also failed to derive reaction time benefit from the interspersed programmed sequence. This was particularly evident on the second run of the task. Overall, patients were learning implicitly at only half the rate of control subjects, corresponding to a large effect size difference between the two groups.

Neuropsychological performance in persons with depression

In accordance with neuropsychological research, patients in this study had moderate to large effect size decrements on the MMSE, motor speed (choice reaction time, visuomotor speed), non-motor speed, perceptual organization, response inhibition and mental flexibility (Veiel, 1997; Naismith *et al*. 2003; Airaksinen *et al*. 2004). Also consistent with prior literature and meta-analytic studies, there were only mild differences in prose passage and list-learning abilities between the groups, corresponding to just over a half standard deviation unit (Burt *et al*. 1995; Veiel, 1997; Naismith *et al*. 2003). There were small to moderate effect size differences on memory retention measures. However, these were not statistically different, possibly due to the sample being out-patients, who may exhibit less memory deficits (Basso & Bornstein, 1999). There was no difference in working memory between the two groups and, consistent with some research, persons with depression did not have poorer verbal fluency or poorer performance on the Tower of London Test and the WCST (Fossati *et al*. 2001; Naismith *et al*. 2003; Airaksinen *et al*. 2004; Butters *et al*. 2004; Stordal *et al*. 2004).

Relationship between IL and neuropsychological impairment

The literature regarding the association between IL and cognition in depression has returned mixed results and has used a variety of tasks with varied neurobiological underpinnings. Additionally, previous IL studies have not examined relationships with neuropsychological function in a detailed manner and have focused on the relationship with explicit memory. In this study, there was no association between IL and absolute measures of explicit (i.e. RAVLT, WMS-R Logical Memory) episodic learning or memory retention. This is consistent with our expectations that IL recruits disparate circuits to those required for explicit memory.

One of the most robust findings to transpire from this study was the relationship between IL and performance on the Trailmaking Test. While TrailsA is primarily a test of visuomotor speed, TrailsB imposes the additional demands of working memory and mental flexibility and has emerged as one of the most consistent and pronounced areas of impairment in persons with depression (Veiel, 1997), sometimes reduced by more than two standard deviations (Naismith *et al*. 2003). Although performance is likely to be mediated by many brain networks, TrailsB may more specifically reflect frontal lobe functioning (Spreen & Strauss, 1998; Broshek & Barth, 2000). Thus, in addition to the finding of impaired IL, suggesting striatal dysfunction, the inter-relationship between poor IL and poor performance on TrailsB serves to

reinforce frontosubcortical theories of depression. This relationship upheld even after adjusting for slowed speed on TrailsA, thus suggesting that it is not simply due to motor speed.

In patients with severe depression, performance on Part A of the Trailmaking Test has been reported to be related to the size of the right caudate nucleus, a key structure in motor, affective and cognitive loops (Naismith *et al.* 2002). Pertinent to the findings here, Rauch *et al.* (1995, 1997*a*, *b*) reported that the right striatum was the area recruited by the IL task in normal and patient samples. Taken together, these data suggest a common link between depression, impaired functioning in the right striatum, and impaired performance on IL tasks and on commonly impaired tests of visuomotor speed and mental flexibility. The relationship between IL and the Trailmaking Test observed in this study therefore validates the use of the motor sequencing task as a measure of cognition in an area that persons with depression typically find challenging.

Relationship between IL and clinical features

In this study there was no association between IL and key clinical features such as age of onset, depression severity or clinician-rated psychomotor change. There was an association between IL and past suicide attempt although in only four people. Consistent with studies suggesting links between cognition and disease duration (Fossati *et al.* 2001; Stordal *et al.* 2004), IL was associated with longer duration of current episode. IL was also associated with severity of acute stressors, levels of which for this sample were, on average, in the moderate range. These results imply that chronicity of the current episode and current life stressors are important determinants of performance and that IL may be reflective of state rather than trait features. Additionally, there was a tendency for performance to be associated with years of illness since disease onset, and for those who had experienced more than a single episode to have poorer performances. Although these relationships were tenuous, they nevertheless suggest that there may be neurodegenerative factors, related to illness duration and recurrence, operative in frontostriatal circuits (Sheline *et al.* 1999; Hickie *et al.* 2005*a*).

Relationship between IL and vascular or biochemical markers

In this small sample, there were not greater rates of vascular disease or biochemical markers (folate, B12, homocysteine) in patients compared with controls. Although there was a tendency for high cholesterol to be related to poorer performance, there were no relationships between vascular risks and IL performance. However, as this study sample was middle-aged with earlier depression onsets and predominantly female, and as few patients had serum folate, vitamin B12 or homocysteine levels outside of the normal range, it is possible that relationships would be attenuated or restricted by the nature of the sample.

Limitations, conclusions and future directions

The examination of IL by motor sequencing tasks in depressive disorders is poorly understood, and no known studies have examined its relationship to such a vast array of variables that potentially underpin pathophysiology. Thus, there was no adjustment for the number of statistical tests used, increasing the risk of Type I error. Interpretation of the results is also precluded by the fact that all patients remained on their usual pharmacological treatment regimes, which may influence both cognition and frontostriatal functioning. Additionally, although functional imaging studies have shown that the IL task recruits the basal ganglia, performance may also be assisted by other brain regions (e.g. the medial temporal lobe) or circuits (e.g. frontotemporal). Similarly, other cognitive processes such as habituation may account for, or influence, the IL effect. Further imaging and cognitive studies would be required to more comprehensively elucidate the contributions of other regions or processes.

Overall, this study suggests that the IL motor sequencing task is a promising tool for probing frontostriatal circuits in depressive disorders, that it is sensitive to impairments and that it correlates with other neuropsychological tests that are most commonly impaired in depression. Future studies using larger samples will allow further analysis of clinical–pathological correlates, neurobiological underpinnings and state *versus* trait markers, and will determine its suitability for predictive, preventative and longitudinal research.

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DECLARATION OF INTEREST

None.

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