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PSYCHOMOTOR FUNCTION AND PSYCHOACTIVE DRUGS

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A cursory review of the literature reveals that the techniques used to assess psychomotor functions are diverse, often complex, frequently insensitive to drug induced changes and sometimes inconvenient to enact or replicate. Adams (1974) used proof reading ability; Croucher & Hindmarch (1974), the duration of the spiral after effect; Betts, Clayton & Mackay (1972), low speed car handling tasks; Malpas, Rowan, Joyce & Scott (1970), card sorting ability; Fargus & Hindmarch (1974), a cardriving simulator; Ashton, Hall, Savage, Telford & Thompson (1972), a pursuit rotor; File & Bond (1979), symbol copying; Van Houten & Zenhausern (1967), the absolute auditory threshold; Davis, Hollister, Overall, Johnson & Train (1976), short and long term memory; Ghoneim & Mewaldt (1977), verbal learning; Gendreau, Sherlock, Parsons, McLean, Scott & Suboske (1972), discrimination conditioning of the eyelid response; Gupta (1974), the kinaesthetic figural after effect; Adamson & Finlay (1966), muscular grip strength; Borland & Nicholson (1974), adaptive tracking; Wittenborn, Flaherty, McGough & Nash (1979), a beam balancing task; Bond & Lader (1972), the digit symbol substitution task; Bernstein, Hughes & Forney (1967), delayed auditory feedback; Veldkamp, Straw, Metzler & Demissianos (1974), ocular convergence; Lahtinen, Lahtinen & Pekkola (1978), the speed of putting caps on ball point pens; Ideström & Cadenius (1963) used tapping speed; Masuda & Bakker (1966), the galvanic skin response; Stitt, Latour & Frane (1977), a hidden word task; Bond & Lader (1973), auditory reaction time; Zimmermann-Tansella, Tansella & Lader (1976), the Gibson Spiral Maze; Hedges, Turner & Harry (1971), the critical flicker fusion frequency; Wittenborn, Flaherty, Hamilton, Schiffman & McGough (1976), a time estimation procedure; Church & Johnson (1979), electro-encephalographic changes; Peck, Adams, Bye & Wilkinson (1976), a digit span test; Landauer, Pococke & Prott (1974), a simple response timer; Holmberg & William-Ollson (1963), used body sway; Malpas & Joyce (1969), the duration of after images; Hindmarch & Parrott (1979), the serial subtraction of numbers; Roth, Kramer & Lutz (1977), the Purdue pegboard; Hindmarch (1979a), the stabilometer; Busch, Klapproth, Lücker & Schmitz (1979), concentration; Hindmarch & Parrott (1978), a concept identification task; Jones, Lewis & Spriggs (1978), a group vigilance task; Bond & Lader (1975), the cancellation of 4's; Jones, Jones, Lewis & Spriggs (1979), category clustering; Aschoff, Becker & Weinert (1975), saccadic eye movements; Gagné & Fleishman (1959), the rudder control test; Fleishman & Hempel (1956), multiple limb co-ordination; Jones (1958), an auditory discrimination test; Hindmarch (1975), the choice reaction time task; Hindmarch (1977a), simulated night time car driving performance; Biehl (1979), actual car driving ability; Wittenborn *et al.* (1979), spontaneous reversals of the Necker cube; Taeuber (1977), two handed cordination; Doongaji, Sheth, Apte, Lakdawala, Khare & Thatte (1979) used Whipple's tracing board and Hindmarch & Clyde (1980a, b), a trigram recognition task.

The foregoing examples of tests of psychomotor function are in no way exhaustive of the diversity of tests which have been used to measure the effects of psychoactive compounds on human behaviour. Each test has its own merits and defects but it can be questioned to what extent each researcher has viewed his approach within a theoretical framework. The major assumption of the psychopharmacologist is that the effects of a drug can be ultimately judged in behavioural terms. However, the range of behavioural activities presented above makes the choice of measure difficult to effect. If psychopharmacology is to be psychologically relevant, the study of the effect of drugs in the context of a well defined model of behaviour must be consistently pursued (Michon, 1973).

The complexity of the relationship between the overt behavioural activity of the organism and the stimulus impinging on the individual at a particular point in time makes the task of providing a reliable and parsimonious model of behaviour most difficult. However, it is possible to isolate the major variables of performance which go to make up the psychological reaction to the administration of a psychoactive substance (Figure 1).

It is obvious that the mode and level of activity of the brain and central nervous system will be

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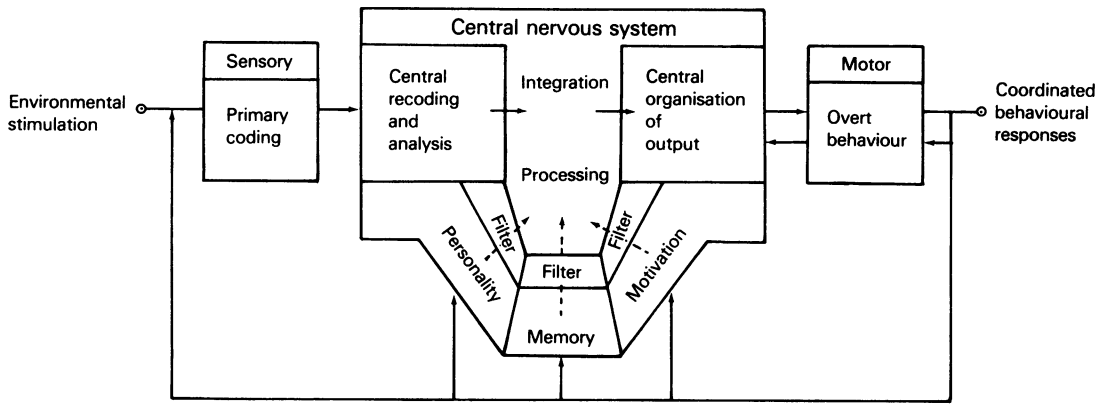


Figure 1 Psychomotor performance results from the co-ordination of sensory and motor systems through the integrative and organisational processes of the brain and central nervous system. The processing of sensory information is influenced by personality, memory and individual motivation, while the overall function of the integrative mechanism is governed by the state of arousal of the central nervous system. Complex feedback and adaptive systems complete the process by which environmental stimuli produce appropriate, co-ordinated behavioural responses.

dependent upon personality, motivation and memory and it is necessary to examine the extent of the effect of these factors on the measurement of performance and to see how such influences might be controlled and minimised.

Eysenck (1963, 1972) and Claridge (1967, 1970) have shown that an inverted U relationship holds between some personality dimensions, e.g. neuroticism, and performance on sensori-motor tasks like the pursuit rotor. The inverted U relationship implies that high neuroticism subjects will have poorer performance than less neurotic ones, because of their personality. Inter-individual differences in performance, due to personality, are well illustrated in the different psychomotor test scores which have been observed in patient and 'normal' volunteer populations (Malpas, Legg & Scott, 1974; Tansella, Zimmermann-Tansella & Lader, 1974). Significant relationships between neuroticism, or anxiety levels, and performance changes with benzodiazepine derivatives have also been reported (Biehl, 1974; Leygonie, Rethone, Yuceyatak & Yuceyatak, 1975), and anxious patients have been shown to have significantly lower critical flicker fusion thresholds than age matched 'normals'. (Krugman, 1947; Goldstone, 1955; Bühler, 1955; Jones, 1958). The effects of personality on performance become more pronounced at the extremes of affectual dimensions. In studies of the effect of a psychoactive drug in normal volunteers, the interaction of personality and performance can be minimised by a pre-selection of subjects i.e. including only those scoring within a standard deviation of the normative score for their age and sex. The Middlesex Hospital Questionnaire (MHQ) (Crown & Crisp, 1970), Eysenck Personality Inventory (EPI) (Eysenck & Eysenck, 1964) and Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch & Lushene, 1968) are all suitable tests for screening subjects. The same principles apply to clinical studies especially where different groups of patients are to be compared. As patients will probably already have impaired psychomotor performance it is most necessary to establish adequate entry criteria to ensure the homogeneity of the experimental group.

Motivational factors can affect the results obtained in performance studies. The intentions of volunteers, the level of payment of subjects and the expectations of the experimenter and subject can all have a profound influence on experimental results (Ayd, 1972). These extraneous variables can only be controlled by the use of double-blind experimental designs, a careful screening of volunteers, the use of experienced experimenters and a thoroughly reasoned protocol to govern the pragmatics of the test situation.

The intrinsic motivation of the task situation is an important determinant of performance. Drug action on a performance measure can also be affected by the nature of the assessment task. Fargus & Hindmarch (1974) were unable to show any decrement of reaction time performance following temazepam 30 mg or placebo in a car driving simulator. However, Hindmarch (1975) was able to show a significant impairment of reaction time produced by temazepam 30 mg in contrast to placebo, on a laboratory based reaction time task. The protocols, dose, regimen and subject populations were similar for both studies and the contrary results are due to the different test situations. The car driving simulator presented the

task in a high interest situation, a computer controlled driving compartment with appropriate noises and movements. On the other hand the laboratory based reaction task was a straightforward light and button assembly with little intrinsic interest.

It is most important to realise that the disruptive effect of a drug on performance could be masked by the 'stimulating' nature of the assessment measure, particularly if the trial is aimed at assessing the safety of a drug in clinical use, e.g. the effects on car driving performance and related risk prone activities encountered by ambulant patients. The sensitivity of the performance measure can be ensured by including a verum, or positive internal control, in the drug treatment regimen along with the unknown compound and placebo. For example, amylobarbitone sodium is known to have sedative effects. If such effects are not obvious on an assessment measure following the experimental use of the drug, then it must be assumed that the test is insensitive and no credence can be given to any findings obtained in such an instance.

Any test of psychomotor performance involving the co-ordination of sensory and motor systems, e.g. the pursuit rotor, will be prone to practice and learning effects as, on repeated administration, the subject acquires the skills that facilitate performance. Standard tests of mental performance e.g. the digit symbol substitution test of the Wechsler Adult Intelligence Scale, (Wechsler, 1955), cannot be used on repeated administration schedules without modification, as many subjects are able to remember the digit-symbol code and so speed their task performance. Practice, learning and the effects of memory on performance measures are relatively easy to control. Prior to entry in a study relying on a sensori-motor measure of performance all subjects must be trained on the task until their 'learning curve' has reached a plateau, i.e. until the response measure has reached a limiting value and maintained such a value for several trials. When subjects are trained to a criterion, where no further increase in performance can be detected, they can then be admitted to a study. Such pre-training can completely eliminate learning effects, as evidenced in the unchanging placebo condition responses found in a model study by Taeuber, Badian, Brettel, Royen, Rupp, Sittig & Uihlein (1979).

In experiments using repeated assessments involving codes, mental arithmetic procedures, memorized material, letter cancellation and similar sequential stimuli it is necessary to change the code or letter to be cancelled or material to be memorized on each test occasion to prevent subjects' remembering or familiarizing themselves with the solution or response code. However, the change in code or letter should not follow any clearly defined sequence but should be random, as some subjects are very adept in 'reasoning out' such patterned variation. This relatively simple procedure for making parallel forms of the same test effectively controls for any memorizing or learning which could otherwise interfere with the performance assessment.

We are now in a position to examine the ways in which the activity of psychoactive drugs on psychomotor performance can be measured. A consideration of Figure 1 shows that there are four essential components of psychomotor behaviour *viz.* the sensory processing aspects, the central integration and processing mechanisms, the overt motor responses and the overall sensori-motor co-ordination. The total psychological response to a psychotropic compound is, as we have seen, a more complex interaction involving personality, motivational factors and even sociocultural habits and expectancies. However, the psychomotor response to a drug is due to the several or conjoint effects of the substance on the components of performance.

The assessment of sensory function and sensory processing ability

Purely sensory measures of the effects of centrally acting drugs have not proved very reliable. Van Houten & Zenhausern (1967) showed that meprobamate significantly affected absolute auditory thresholds but the direction of the change was not consistent. Wittenborn (1979) found no test of auditory perception to discriminate between the actions of various benzodiazepines and placebo. On the other hand, Evans, Martz, Rodda, Kiplinger & Forney (1974) showed an increasing impairment of delayed auditory feedback to be commensurate with an increase in blood alcohol concentration but Bernstein *et al.* (1967) were unable to show any differences between placebo and medazepam 10 mg on a colour naming task under delayed auditory feedback.

Suzumura (1968) developed a kinetic visual acuity test which Roden, Harvey & Mitchard (1977) showed to be sensitive to the effects of alcohol alone and alcohol in combination with either nitrazepam or methaqualone and diphenhydramine (Mandrax). Veldkamp *et al.* (1974) showed ocular convergence to be impaired by triazolam 0.5 and 1.0 mg and Aschoff *et al.* (1975) found saccadic velocity reduced by diazepam 10 mg but not by sulpiride 100 mg. A study by Gendreau *et al.* (1972) using the classical conditioning of the human eyelid response differentiated methamphetamine 20 mg from both placebo and diazepam 20 mg because of the observed improvement in discrimination produced by the psychostimulant. Gupta (1974) showed stimulant (dexamphetamine, 10 mg) and depressant (pheno-

barbitone, 100 mg) drugs could be discriminated on the duration of the kinaesthetic figural after effect, while Malpas & Joyce (1969) found that nitrazepam 5 and 10 mg increased the latency and shortened the duration of visual after-images.

Although some of these tests of sensory function are discriminating of the action of psychoactive drugs, they have limited usefulness and replicability due to the interaction of personality variables (Eysenck & Easterbrook, 1960) and inter-subject processing differences (Gray, 1967) with the performance scores obtained.

Detection, perception and recognition of a stimulus are three levels of information processing which together account for the majority of the sensory activity of the organism (Mashour & Devine, 1977). Changes in the level of activity of the sensory input brought about by the administration of a drug can have a disruptive effect on total psychomotor performance and reduce the responsiveness of an individual to changes in his environment.

Changes in stimulus detection performance or vigilance have been produced by a variety of psychoactive drugs e.g., hyoscine and meclozine (Colquhoun, 1962), methylphenidate (Cohen, Douglas & Morgenstern, 1971), chlorpromazine and secobarbital (Kornetsky & Orzack, 1964), amphetamine (Mackworth, 1965); bromazepam (Saario, 1976), diazepam (Kleinknecht & Donaldson, 1975) and clobazam (Wittenborn *et al.*, 1979).

Orzack, Taylor & Kornetsky (1968) devised a non-motivated continuous attention task given over a 3 h period. Subjects were required to press the key which matched a number display, the motor component was small and the task not paced. The number of errors made following magnesium pemoline 50 mg, caffeine 200 mg and methylphenidate 15 mg were all significantly less than those produced by placebo, showing the central stimulating activity of the three drugs. In the continuous attention task of Rosvold, Mirsky, Sarason, Bransome & Beck (1956) subjects have to detect a critical stimulus, usually a letter X, from random sequences of letters presented at a constant rate. Using this procedure Mirsky & Kornetsky (1964) were able to distinguish the activity of phenothiazines from the action of barbiturates. Wittenborn *et al.* (1979) describe both a simple and a complex vigilance task. The latency of the subjects' responses to the critical stimulus, as well as the errors made, are scored in both tests. The tests have proved sensitive enough to discriminate between the effects of different benzodiazepines (*op. cit.*). However, the use of letter stimuli and the task requirements of the conjoint recognition of two elements will involve higher mental coding processes. Observed drug effects can not then be directly attributed to disturbance of a sensory process alone. To avoid the interaction of coding and attentional systems with letter recognition, Williams, Lubin & Goodnow (1959) produced an auditory version of the continuous performance test which was later refined and developed by Wilkinson (1968) into one of the most sensitive tests of vigilance. Subjects listen to 1kHz tones of 82dB against a background white noise of 76dB. The duration of the tone is usually 0.5 s but shorter tones of 0.4 s are randomly presented as critical stimuli to be recognized by pressing a button. Hart, Hill, Bye, Wilkinson & Peck (1976) showed the number of correct detections was significantly reduced by diazepam 2.5 mg, while Bye, Munro-Faure, Peck & Young (1973) found a significant improvement in the auditory vigilance task following dexamphetamine in a dose range 1 mg to 7.5 mg. The sensitivity of the task and the separation of the effects of sedative and stimulant drugs make it a most useful screen for potential psychotropic agents. Bye *et al.* (1973) were able to conclude that 1-benzyl-piperazine had psychostimulant actions because of its similar profile of action to dexamphetamine on the auditory vigilance task. Peck, Bye, Clubley, Henson & Riddington (1979) found that amitriptyline 25 mg impaired auditory vigilance but that bupropion 50 and 100 mg a potential antidepressant was indistinguishable from placebo in a study where dexamphetamine 5 and 10 mg, as a positive internal control, improved performance. In a study of the effects of nitrazepam 5 and 10 mg on sound and light sleepers Peck, Bye & Claridge (1977) found that the auditory vigilance of sound sleepers was unaffected by the drug treatment. However, light sleepers had an impaired performance the morning following nocturnal treatment with nitrazepam 10 mg but not following 5 mg.

Millar (1979) investigated the change of vigilance efficiency through the day following placebo, chlorpheniramine 10 mg and chlorpheniramine 10 mg plus ephedrine 15 mg. There was a significant contrast between the two drug conditions. Chlorpheniramine alone exhibited the sedative activity characteristic of an antihistamine and impaired vigilance. The addition of ephedrine to chlorpheniramine counteracted the effect and the combination was no different to placebo in its action on vigilance efficiency.

The perceptual processing of sensory information can be readily assessed by using a letter or number cancellation task, providing the motor component is not too great. Bond, James & Lader (1974a) provide a typical example of a number cancellation task where the number to be checked appears 40 times in 400 digits. Zimmermann-Tansella *et al.* (1976) have shown an adverse effect on cancellation 12 h after chlordesmethyldiazepam 1 and 2 mg. Cancellation tasks seem to be quite sensitive to low doses of sedative drugs as File & Bond (1979) found lorazepam 1 and 2.5 mg to reduce the total numbers

cancelled in a 90 s period. Letter cancellation scores of subjects treated with diazepam 5 mg were significantly worse than those of subjects receiving placebo (Lawton & Cahn, 1963). Bond & Lader (1972) found the hypnotic nitrazepam 5 and 10 mg decreased the rate of cancellation when compared to placebo while both Stitt *et al.* (1977) and Jones *et al.* (1978) showed a significant impairment of letter search and cancellation tasks following diazepam 5 mg. Consroe, Carlini, Zwicker & Lacerda (1979) found the interactive effect of cannabidiol and alcohol to reduce performance on a cancellation test.

However, Bond & Lader (1975) were unable to show any significant effect of flunitrazepam 1 and 2 mg on a number cancellation task and Hindmarch & Clyde (1980a) found a letter cancellation task insensitive to the effects of a benzodiazepine hypnotic, HR158. In an attempt to increase the sensitivity of the letter cancellation task Hindmarch & Gudgeon (1980) had subjects cancel 1, 2, 3, or 4 letters from pages of random letters. The low information processing loads involved in cancelling 1 or 2 letters did not enable any discrimination to be made between lorazepam 1 mg, clobazam 10 mg or matching placebo 1 capsule, each given three times daily for 3 days. However, significant impairments of perceptual processing compared to placebo were found following repeated doses of lorazepam 1 mg when higher information loads, i.e. the cancellation of four letters, were used.

Recognizing sensory information involves the matching of the perceptual figuration with a pre-existing or stored stimulus pattern. The identification of current information and matching with previously stored patterns is obviously a function of the central sensory recoding and processing systems. Stroop (1935) drew attention to an anomalous feature of this recoding mechanism when he found that there was a large disruption and delay in colour naming when letters of one colour were formed into the name of an incongruous colour. This so called Stroop Phenomenon, i.e. a delay in colour naming under the unusual stimulus processing conditions described above, has been widely used in the study of personality (Uherík, 1973), perceptual (Shor, 1971), cognitive (Schiller, 1966), and response (Dyer, 1973) processes. The latency of the colour name response under Stroop conditions has been neglected as a measure of sensory performance within psychopharmacology. This is unfortunate as it would seem to be a reliable and sensitive index of the effect of psychoactive drugs on cognitive and perceptual systems. An interaction between Mandrax and alcohol was demonstrated (Roden *et al.*, 1977) using a Stroop test, but no interaction between nitrazepam and alcohol could be shown. Nakano, Gillespie & Hollister (1978) used a mirror drawing and a Stroop test in an experimental model of anxiety to investigate the effects of nabilone 2 mg and diazepam 5 mg; anxiety was reduced by both drugs.

Ambiguous figures with two distinct perspectives, as in the 'falling staircase' or Necker cube, also provide an assessment measure for sensory processing ability. Wittenborn *et al.* (1979), using the spontaneous reversals reported by subjects while gazing at a Necker cube for a 1 min period, were able to show an impairment of processing following diazepam 5 mg. More interestingly they were able to discriminate between the effects of clobazam 10 mg and diazepam 5 mg on the Necker cube reversal rate the former drug was no different to placebo while diazepam 5 mg significantly reduced the reversal rate.

It is convenient to discuss the effects of drugs upon time judgment under the central coding of sensory information without entering into any debate as to the neurological or psychological basis of temporal estimation. Frankenhaeuser (1959), Goldstone, Boardman & Lhamon (1958), Hornia (1956) and Goldstone & Kirkham (1968) have all shown consistent findings with central depressants and stimulants and the subjective estimation of time. Amphetamines and related stimulants produce a subjective over estimation of a standard time interval while barbiturates produce an under estimation. Wittenborn *et al.* (1976, 1979) have used the estimation of short temporal intervals, 8–15 s, in their studies of benzodiazepines and antidepressants. The natural tendency to over estimate the time required to produce a short time interval, without the benefit of a standard, was reduced by prazepam 30 mg and imipramine but not by clobazam 10 mg three times daily. The reduction of the 'normal' over estimate by prazepam and imipramine is evidence of their sedative activity on temporal processing.

Recoding and recognition of sensory information is well illustrated in the performance of the digit symbol substitution test. The DSST forms part of the performance scale of the Wechsler Adult Intelligence Test (Wechsler,1955), and many researchers have used it to measure drug activity on perceptual coding skills. There is a motor component in the task but as the principal determinant of performance is the recoding of visual information we will consider the DSST here.

Table 1 shows that the DSST is a useful indicator of drug produced changes in sensory processing performance. The use of parallel forms for repeated administration is necessary to avoid interference from practice and learning effects.

The assessment of CNS function and central processing ability

A consideration of the psychomotor performance model shows that there are two major components of

central nervous system activity, *viz.* integration and processing. We must also consider drug effects on memory and learning as these two systems have an extensive influence in determining the overall activity of a psychoactive substance on the brain and central nervous system.

Central integration

The relationship between the electrical activity of the brain as measured on the electroencephalogram and cognitive behaviour is, as yet, unclear. However, the development of techniques correlating drug induced changes in behaviour with electrophysiological changes in EEG variables (Goldstein & Stoltzfus, 1973), and the evoked potential (Näätänen, 1975), will no doubt provide, in the future, the most sensitive index of central nervous system activity. For example, Saletu & Taeuber (1980) used EEG for the assessment of antidepressant drug effects and found the pharmacokinetics of nomifensine did not correspond with the pharmacodynamics of the drug in producing changes in brain activity.

There have been many attempts at measuring the level of arousal or integration potential of the CNS. Guest, Duncan & Lawther (1970) used auditory flutter fusion threshold, Croucher & Hindmarch (1974) and Saletu & Grunberger (1979) used the duration of the spiral after effect. Marjerrison, Neufeldt, Holmes & Ho (1973) measured integrated EEG amplitude and two flash threshold and Smith & Misiak (1976) reviewed 33 studies which used the critical flicker fusion threshold to assess the changes in CNS arousal produced by a variety of psychotropic agents.

It is this last measure that must be regarded as the assessment of choice for investigating the change in overall integrative activity of the CNS produced by psychoactive drugs.

Smith & Misiak (1976) found the CFF threshold to be altered to a statistically significant degree ($P<0.05$) in 65% of the studies they reviewed. They concluded that stimulants (amphetamines) increased the threshold and sedative-hypnotics (barbiturates, chloral hydrate, glutethimide) reduced the threshold. As with all review papers, the authors found difficulty in making absolute conclusions since the various studies employed different methodologies, controls, treatment regimens and subjects. Table 2 presents findings from studies published since, or not included in, the review.

These later studies confirm the general findings relating to stimulant and sedative drugs but also show the general sedative activity of the 1, 4 benzodiazepines which was somewhat equivocal in the earlier papers.

As yet there does not exist any standard for the rating of an individual's absolute CFF threshold so the technique should be used only for the monitoring of drug induced change. The CFF measure is dependent upon a number of experimental variables (Keesey, 1970), including ambiant illumination, size of image, luminance of stimulus, viewing distance and pupil size. The easiest way to control the majority of these variables is to fix the conditions under which the measurement takes place and to hold them constant

Table 1 Performance on the DSST task following treatment with a variety of drugs, showing the sensitivity of the measure to the effects of sedative compounds

Studies where an impairment of DSST performance was found following psychoactive medication		
Amylobarbitone	50 and 100mg	Hart *et al.* (1976)
Flunitrazepam	1 and 2mg	Bond & Lader (1975)
Flurazepam	15mg	Bond & Lader (1973)
	30mg	Bond & Lader (1973); Church & Johnson (1979)
Nitrazepam	5mg	Bond & Lader (1972); Malpas (1972)
	10mg	Malpas & Joyce (1969); Walters & Lader (1971); Bond & Lader (1972); Malpas (1972); Peck *et al.* (*1977*)
Diazepam	5mg	Hart *et al.* (1976)
	10mg	Jäättelä *et al.* (1971)
	17–28mg	Shira (1978)
Chlordiazepoxide	20mg	Shaffer *et al.* (1963); Besser & Steinberg (1967)
Lorazepam	1 and 2.5mg	File & Bond (1979)
Imipramine	50mg	Wittenborn (1977)
Studies where an improvement of DSST performance was found following treatment		
Clobazam	10mg	Salkind *et al.* (1979)

Table 2 The sensitivity and range of the CFF measure as an index of drug activity on the central nervous system is shown in the changes, against placebo, found in the above studies

Drugs producing a reduction in CFF threshold		
Chlorpromazine	25mg	Turner (1973)
	50mg	Parrott & Hindmarch (1975a,c)
Haloperidol	1mg	Parrott & Hindmarch (1975c)
Doxepin	25–75mg	Grundström *et al.* (1977)
Mianserin	15mg	Fink *et al.* (1977)
	10 and 20mg	Crome & Newman (1978)
Mianserin + alcohol	10mg + 0.5g/kg	Seppälä (1977)
Amitriptyline + alcohol	25mg + 0.5g/kg	
Amitriptyline + chlordiazepoxide	25mg + 10mg	Hindmarch *et al.* (1980)
Meperidine	75mg	Korttila & Linnoila (1975)
Phenobarbitone	100mg	Guest *et al.* (1970)
Quinalbarbitone	100mg	Turner (1973)
Amylobarbitone	100mg	Hindmarch (1975, 1976b, 1979a, c); Parrott & Hindmarch (1975a, b); Turner (1973)
Promethazine	25mg	Turner (1973)
Chlorpheniramine	4mg	Hindmarch & Parrott (1978b)
Ethanol	0.7g/kg	Tarter *et al.* (1971)
	0.48 – 0.67g/kg	Rosketh & Lorentzen (1954)
	0.8g/kg	Ideström & Cadenius (1968)
	0.32 – 1.29g/kg	Enzer *et al.* (1944)
	0.63 – 0.8g/kg	Goldberg (1943)
	0.44g/kg	Rizzo (1957)
Chlordiazepoxide	10mg	Hindmarch (1979a)
Diazepam	5mg	Hedges *et al.* (1971) Hindmarch (1979a)
	7.5 – 22.5mg	Grundström *et al.* (1978)
	8.8 – 22.8mg	Haffner *et al.* (1973)
	10mg	Mørland *et al.* (1974); Korttila & Linnoila (1975); Seppälä *et al.* (1976)
Medazepam	15mg	Seppälä *et al.* (1976)
Oxazepam	20 and 40mg	Molander & Duvhök (1976)
Lorazepam	0.5mg	Hedges *et al.* (1971)
	1mg	Hedges *et al.* (1971); Turner (1973)
	2.0mg	Ogle *et al.* (1976); Farhoumand *et al.* (1979)
	2.5mg	Seppälä *et al.* (1976)
Temazepam	30mg	Hindmarch (1975, 1976a, 1979c)
Nitrazepam	5mg	Hindmarch (1975)
	5 – 15mg	Grundström *et al.* (1978)
	10mg	Fell *et al.* (1973); Hindmarch & Clyde (1980b)
Drugs producing an elevation of CFF threshold		
Amphetamine	10mg	Parrott & Hindmarch (1975b)
	15mg	Turner (1973); Taeuber *et al.* (1979)
Methylphenidate	20mg	Parrott & Hindmarch (1975a, b)
Phenmetrazine	25 and 30mg	Turner (1973)
Diethylproprion	25mg	Turner (1973)
Pemoline	20mg	Parrott & Hindmarch (1975b)
Dimethylxanthine	400mg	Parrott & Hindmarch (1975b)
Hydergine	12mg	Hindmarch *et al.* (1979)
Nomifensine	25mg	Hindmarch *et al.* (1980)
	75mg	Hindmarch & Parrott (1977)
Nomifensine + clobazam	25 + 7.5mg	Hindmarch *et al.* (1980)
Clobazam	10mg	Hindmarch (1979a, b)
	20mg	Hindmarch & Parrott (1980b)
	30mg	Hindmarch & Parrott (1979)

from test to test. Repeated measures of the threshold should be taken using one of the standard psychophysical methods; e.g. limits, paired comparison or frequency to collect the data (Woodworth & Schlosberg, 1958).

Changes in pupil diameter will result in alteration of the CFF threshold due to the change in retinal illumination. This pupillary change of CFF threshold could well mask any drug induced change in brain activity but the use of an artificial pupil, a 2 mm viewing aperture, will control such effects.

As individual CFF thresholds vary due to personality, motivational state and circadian cyclicity it is best to use each subject as his own control and to ensure that repeated testing is conducted at the same time of day—safeguards which apply to all psychometric assessments.

Central processing

The range of tasks to assess mental performance as processing ability is extensive. A concept identification task has been used in several studies (Hindmarch & Parrott, 1978; 1979; 1980a; 1980b) but performance ratings were found to be too dependant upon the experience of the test administrator to warrant the more general usage of such a measure. Symbol arrangement (Liljequist, Seppälä & Mattila, 1978) has proved to be a less sensitive test than either the DSST or symbol cancelling tasks described earlier.

Symbol copying as employed in studies by File & Bond (1979) and Bond & Lader (1973; 1975) is sensitive to drug induced changes but practice and learning effects make the results obtained variable. The most reliable and certainly the easiest way of measuring cognitive 'processing' ability is by an arithmetic or number handling task. Bond, James & Lader (1974a, b), Ashton *et al.* (1972) and Keuchel, Kohnen & Lienert (1979) used arithmetic addition tasks to show changes in performance due to amylobarbitone, oxypertine, and nicotine and caffeine respectively. Masuda & Bakker (1966) showed mathematical performance was reduced by diazepam 10 and 20 mg and similar impairments following repeated doses of diazepam 10-20mg were found by Frostad *et al.* (1966). Using the serial subtraction of numbers technique Hindmarch (1977b) was able to show the sedative effects of flunitrazepam 1 mg and flurezepam 15 mg. Disruptive effects and a lowering of task performance have also been shown using the sequential subtraction of numbers technique following clorazepate 15 mg, Hindmarch & Parrott (1979); lorazepam 1 mg, Hindmarch & Gudgeon (1980); triazolam 0.5 mg and nitrazepam 10 mg, Hindmarch & Clyde (1980b); HR158, a benzodiazepine hypnotic at doses of 1 and 2 mg, Hindmarch & Clyde (1980a); and amitriptyline 25 mg with chlordiazepoxide 10 mg, Hindmarch *et al.* (1980). Taeuber *et al.* (1979) found that nomifensine 100 mg increased the number of correct solutions obtained on a continuous arithmetic calculation test compared to placebo.

In numerical ability tests measurement of the time taken to complete the task and the number of errors made enables the separation of the effects of psychostimulants, which shorten task latency but increase the errors made, from the action of drugs which improve performance, i.e. shorter task latency without increasing errors. The two response measures also enable individual differences to be observed as some subjects sacrifice accuracy for speed. The confounding effects of individual styles on arithmetic tasks are controlled by careful instructions to the subjects and adequate pre-experimental training.

Memory and learning.

It is not proposed to enter a debate as to the theoretical basis for distinguishing between long and short term memory. A parsimonious definition of short term memory (STM) would indicate that it is a limited capacity store of processed information which functions for a variable time period, dependent on the demands of the task situation, to assist stimulus recognition and processing. Items in the STM store can be easily displaced by new stimuli or information. The likelihood of STM store being disrupted by new stimuli and the decay of the memory trace are the basis of most tasks designed to measure the effects of drugs on short term recognition or recall of learned information. A consideration of some relevant tasks and comments on methodology are given in a useful paper by Squitieri, Mazzola, Lazzari, Cervone & Agnoli (1977). Short term memory can be conveniently measured using the digit span technique of the Wechsler Adult Intelligence Test (Wechsler, 1955). It should be remembered that scores on digit span measures do relate to intelligence and mental performance ratings and subjects should, therefore, act as their own controls when such assessments are made.

Miller & Dolan (1974) were able to show the disruptive effect of alcohol, 1.2 mg kg^{-1} body weight, on a WAIS digit span test and Davis *et al.* (1976) showed a significant decrement in STM following physostigmine 3 mg. Digit span measures also showed an impairment of STM following both hyoscine 0.3 mg and nitrazepam 5 mg (Jones *et al.*, 1979). Haffner, Mørland, Setekleiv, Strømsaether, Danielsen, Frivik & Dybing (1973) found diazepam 10 and 20 mg to impair STM and Shira (1978) showed diazepam 17 to 28 mg to produce STM deficits. Anterograde amnesia has been found (Clarke, Eccersley, Frisby & Thornton, 1970) following intravenous diazepam 0.24 mg/kg and

Ghoneim, Mewaldt & Thatcher (1975) found immediate and delayed recall of words significantly impaired following diazepam 20 mg.

The lack of impairment of digit span performance following chlordiazepoxide 10 and 25 mg (Ogle & Ditman, 1966) and meprobamate 800 mg (Melikian, 1961) is due to differences in experimental protocols between these two studies and those more recent investigations given above.

The learning and subsequent recall or recognition of words, numbers and nonsense trigrams have been widely used to test the effects of drugs on immediate memory. Performance on four short term retention tasks was impaired following whisky 2 ml/kg body weight (Dornič, Myrsten & Frankenhæuser, 1971), and File & Bond (1979) showed lorazepam 1 and 2.5 mg interfered with the learning and retention of random digits. Using free recall and recognition of word lists Ghoneim & Mewaldt (1977) concluded that injected diazepam 0.3 mg/kg and scopolamine 8 mg/kg impaired the learning of new information. More esoteric measures of verbal rote learning (Andersson & Post, 1972; Andersson & Hockey, 1975) have been able to detect the effects of cigarette smoking on performance efficiency. Using verbal conditioning procedures, Gupta (1973) has separated the facilitatory effect of dexedrine from the inhibitory activity of chlorpromazine and phenobarbitone. Using both digit span and paired-associate learning techniques Liljequist *et al.* (1978) have shown that amitriptyline 25 mg, but not mianserin 10 mg or placebo impaired performance.

The inconsistencies between some of the results from different studies on digit span assessments are due to different methodologies and test conditions for Andersson (1975) has shown that STM performance can readily be affected by task induced arousal and situational novelty. However, with suitable controls for experimental variations it would seem that digit span and verbal material as employed by Brown, Lewis, Brown, Horn & Bowes (1978) are useful measures for estimating drug activity on short term memory and/or learning processes.

The assessment of motor function and behavioural co-ordination

Motor activity and co-ordination can be classified under four headings, *viz.* ballistic, gross body balance, fine motor control and motor manipulative activity. Centrally acting drugs have been shown to affect performance on measures of each type of motor activity.

Ballistic activity

The rate of finger tapping is one of the simplest of human motor activities and has been widely used to measure drug changes of motor performance. Even this simple task is subject to other than drug induced changes of which prospective users should be aware. Wilson, Tunstall & Eysenck (1971) have shown clear motivational and personality variables operating on finger tapping performance especially if the time on the task is prolonged. These extraneous variables should be isolated by limiting the test tapping period to a maximum of 60 s.

Most studies have used the technique described by Frith (1967) and tapping performance has been shown to be impaired following nitrazepam 10 mg (Peck *et al.*, 1977), diazepam 10 mg (Černý *et al.*, 1973; Ghoneim *et al.*, 1975), butobarbitone 200 mg (Walters & Lader, 1971), flurazepam 30 mg (Salkind & Silverstone, 1975), oxazepam 10 mg (Di Mascio & Barrett, 1965) and nitrazepam 5 and 10 mg (Bond & Lader, 1972). Černý *et al.* (1973) have also shown that methylphenidate 20 mg significantly increases tapping performance compared to placebo, and Zimmermann-Tansella *et al.* (1976) have suggested that tapping rate is facilitated by chlordesmethyl-diazepam 1 mg. Although these findings suggest that finger tapping is useful in discriminating performance across the sedative—stimulant range of psychoactive drugs, Vogel (1979) found 19 of 22 instances of tests of finger tapping with a range of 7 anxiolytic drugs to show no placebo contrasted effects.

Gross body movement

The ability to walk along a straight line without undue deviation is a well known assessment of the effects of alcohol on body movement and balance systems. This simple assessment has not been widely used in experimental situations although Korttila, Saarnivaara, Tarkkanen, Himburg & Hytonen (1978) report its usefulness in monitoring the residual effects on sedation of diazepam and flunitrazepam used during bronchoscopy.

The stabilometer is the most widely used assessment of body movement. It is a motor learning task (Wade & Newell, 1972) in which a subject has to balance on a pivoted support. Taeuber *et al.* (1979) provide details of an automated body sway test and Wittenborn *et al.* (1979) details of a balance beam procedure which fulfil the same purpose as the stabilometer. Hindmarch (1979a) found both nitrazepam 5 mg and clobazam 20 mg significantly increased the balance time compared to placebo on a stabilometer test, but attributed these findings to the effectiveness of the drugs in reducing the perceived effects of physical fatigue inherent in that particular test. Wittenborn *et al.* (1979) found fewer instances of missteps using the balance beam technique following clobazam 10 mg than either placebo or diazepam 5 mg, and Taeuber *et al.* (1979) showed their body sway technique to be sensitive to the interaction of

clobazam and alcohol. Orr, Dussault, Chappel, Goldberg & Reggiani (1976) found a clear impairment of standing steadiness following both 10 and 20 mg diazepam. Penttilä, Lehti & Lönnquist (1975) demonstrated the usefulness of stabilometer measures in screening patients for psychotropic effects and Evans *et al.* (1974) have shown the wobble board to be sensitive to alcohol induced impairment of body movement. Orr *et al.* (1976) found high dose related correlations between diazepam produced changes on stabilometer performance and drug plasma levels.

Fine motor control

Using a hand steadiness task and a Whipple Tracing Board, Doongaji *et al.* (1979) were able to show improved motor co-ordination following repeated dosing with clobazam 10 mg in a group of anxious patients. Trail making tests (Reitan, 1958) have shown both dexamphetamine 30 mg/kg body weight and psilocybin 0.2 mg/kg impair trail making performance (Duke & Keeler 1968). A variety of writing speed tasks have been shown to be sensitive to both stimulant and sedative drugs (Nash & Stone, 1974), and hand steadiness has been shown to be sensitive enough to discriminate the effects of pemoline and caffeine (Henert & Janke, 1957).

Motor manipulation

Pegboard and 'rivet with washer' techniques provide reasonable measures of motor manipulative skill. May, Childs & Urquhart (1976) found the performance of alcoholics on manipulative tests was significantly impaired and Knights & Hinton (1969) found a pegboard completion task sensitive to the effects of methylphenidate in children with learning problems. Roth *et al.* (1977) used a pegboard in an evaluation of the side effects of flurazepam, triazolam and secobarbital. Differences between the drugs on sleep variables were found to be consistent with the differences obtained on the pegboard and related measures. Lahtinen *et al.* (1978) using simple motor manipulations were able to show an impairment of performance following both 5 and 10 mg nitrazepam and Lawton & Cahn (1963) found pegboard performance reduced by diazepam 5 mg, but Hindmarch & Gudgeon (1980) were unable to detect changes in pegboard performance following repeated doses of lorazepam 1 mg, clobazam 10 mg and placebo although the two drugs were clearly differentiated by other tests administered at the same time.

In general measures of motor function are contaminated by the great inter-individual differences in performance which exist prior to the administration of a drug. Statistical control of between subject differences in pre-experimental performance can be effected through the use of analysis of covariance, but there is no better way of minimizing such differences than the adequate training of experimental subjects prior to the commencement of an investigation.

The assessment of sensori-motor performance

The co-ordination of sensory and motor systems is the basis of most skilled behaviours. It is easier to develop laboratory analogues of everyday behaviour than to control the real life situation to the level necessary for obtaining reliable information about drug interaction with performance skills. However, Harper & Kidera (1972) tested flurazepam and glutethimide in a twin-turbo jet flight simulator and found that both drugs impaired performance. Haward (1968) also showed improvement of concentration on an air traffic control simulation following phenytoin sodium 150 mg. In car handling tasks Betts *et al.* (1972) showed performance decrements following chlordiazepoxide 10 mg but using similar tasks Hindmarch, Hanks & Hewitt (1977) were unable to show any decrement in performance due to the administration of clobazam 20 mg nocte for six nights or clemastine 1 mg twice daily for three days (Hindmarch, 1976a).

Recent studies using similar low speed car handling tasks have shown significant performance impairments produced by lorazepam 1 mg three times daily for 3 days (Hindmarch & Gudgeon, 1980) and by chlordiazepoxide 10 mg with amitriptyline 25 mg three times daily for 2 days (Hindmarch, Parrott & Stonier, 1980). Biehl (1979) using dual control cars in traffic was able to show that diazepam 10 mg significantly impaired subjects' brake response readiness while clobazam 20 mg produced a significant increase in responsiveness compared to placebo values. Berry, Burtles, Grubb & Hoare (1974) found clobazam 10 mg did not increase brake reaction time although diazepam 10 mg produced a significant increase compared to placebo. Although there is great inter-study variability there is also consistency in the findings of impaired performance of real life tasks following sedative drugs. Such impairment emphasises the accident risks patients prescribed such drugs might encounter in the everyday work situation (Edwards, 1978).

Sensori-motor activity has also been assessed on a variety of tasks which have some relevance to performance of real life activities, particularly car driving. Linnoila & Hakkinen (1974) found that diazepam 10 mg caused professional drivers to 'collide' significantly more frequently than when treated with placebo, on a car driving simulator. On a set of skills related to car driving Seppälä, Korttila,

Häkkinen & Linnoila (1976) found that diazepam 10 mg, medazepam 15 mg and lorazepam 2.5 mg all produced significant impairments of one or more experimental measures when compared to placebo. Korttila (1977) showed lack of impairment of driving related skills following intramuscular injection of prilocaine or mepivacaine but found impairments following lidocaine, bupivacaine and etidocaine. Korttila, Tammisto, Ertama, Pfaffli, Blomgern & Hakkinen (1977) also showed an impairment of driving skills following halothane anaesthesia. Liljequist & Mattila (1979) were able to demonstrate the impairment of co-ordination and reaction time following nitrazepam 10 mg and temazepam 10 and 20 mg while Palva & Linnoila (1978) found that the main metabolites of chlordiazepoxide and diazepam significantly enhanced alcohol induced impairment of psychomotor tasks relating to car driving.

Landauer *et al.* (1974) failed to show any impairment of simulated car driving following 10 or 20 mg medazepam and Dureman & Norrman (1975) failed to find any impairment of simulated car driving after diazepam 15 mg or clorazepate 30 mg. However, the inter-subject pre-test differences in performance were not controlled in the first study and a patient population of neurasthenic, vegetative neurotics were subject to a 3 h testing sequence in the second investigation. It is most likely that such experimental artefacts have interfered with drug effects in these instances as, in general, tests of psychomotor skills related to car driving are sensitive to both psychostimulant and sedative drug activity.

The most basic measure of visuo-motor performance is the pursuit rotor or its pencil-and-paper counterpart, the spiral maze. Performance on these tasks is subject to practice effects which must be carefully controlled and personality has been shown to determine pursuit rotor scores (Eysenck, 1972). None of the 10 studies reviewed by Vogel (1979) showed any change in pursuit rotor performance following chlordiazepoxide 10–15 mg, diazepam 5–10 mg, meprobamate 200–800 mg, prazepam 10 mg and medazepam 10 mg. Salkind, Hanks & Silverstone (1979) found that pursuit rotor performance was significantly improved by placebo in a group of anxious patients showing the clear effects of practice but Salkind & Silverstone (1975) found impairment of tracking following 30 mg flurazepam. In a three way comparison of hexobarbital 250 mg, caffeine 200 mg and pemoline 40 mg against placebo, Busch *et al.* (1979) found no significant changes in pursuit rotor performance although there were drug effects observable on other tests of concentration and memory. Dexamphetamine 5 mg and etifoxine 300 mg have both improved pursuit rotor performance compared to placebo (Córsico *et al.*, 1975). Ogle *et al.* (1976) found propranolol 240 mg, diazepam 5 mg and lorazepam 2 mg to significantly impair pursuit rotor performance. Ashton *et al.* (1972) showed oxypertine 20 mg reduced the time on target in a pursuit rotor task and Macleod, Giles, Patzalek, Thiessen & Sellers (1977) showed impairment after alcohol and diazepam mixtures and Evans *et al.* (1974) for alcohol alone. However, the pursuit rotor cannot be regarded as a reliable index of drug effects on the visuo-motor system unless practice effects are controlled.

The Gibson spiral maze (Gibson, 1965) has been used with a certain degree of success to detect performance changes produced by diazepam in anxious patients (Zimmermann-Tansella *et al.*, 1978). As with the pursuit rotor, practice effects on repeated administration over a short time period make the spiral maze too unreliable to discriminate other than profound sedatives and psychostimulants from placebo. Bond *et al.* (1974a) found it insensitive to the performance differences of anxious and volunteer populations.

The adaptive tracking task is a more refined pursuit and tracking test, which has been shown by Borland & Nicholson (1974) to be sensitive to the effects of heptabarbitone 200, 300 and 400 mg, and Nicholson (1979) has shown the residual sedative activity of flurazepam 30 mg, nitrazepam 10 mg, oxazepam 30 and 45 mg, temazepam 20 mg and diazepam 10 mg. Muller-Oerlinghausen, Bauer, Girke, Kanowski & Goncalves (1977) have also used adaptive tracking tests to detect the impairment of performance produced by lithium salts in both patient and volunteer populations. It is clear that adaptive tracking is a reliable index of the effects of sedative drugs.

Other visuo-motor tasks e.g. the automated rotated designs test (Sambrooks, Macculloch, Birtles & Smallman, 1972: Sambrooks, Macculloch & Rooney, 1975) and the continuous performance reading task (Stern, Bremer & McClure, 1974) have been used too infrequently for any estimate of their sensitivity to drug induced changes in performance to be made.

Card sorting is an excellent example of a performance task which embraces sensory, motor and central components. Berry, Gelder & Summerfield (1965) provide an excellent description of the experimental methodology of a card sorting task using conventional playing cards where task difficulty can be manipulated by altering the complexity of the sorting criteria. It is possible, using the card sorting technique, to isolate changes in performance due to motor activity alone. Card sorting assessments are widely used and sensitive to a range of psychoactive drugs. Zimmermann-Tansella *et al.* (1976) showed card sorting to be impaired following chlordesmethyldiazepam 10 and 20 mg and Tansella *et al.* (1974) found similar impairment with N-desmethyldiazepam 20 mg. Malpas & Joyce (1969)

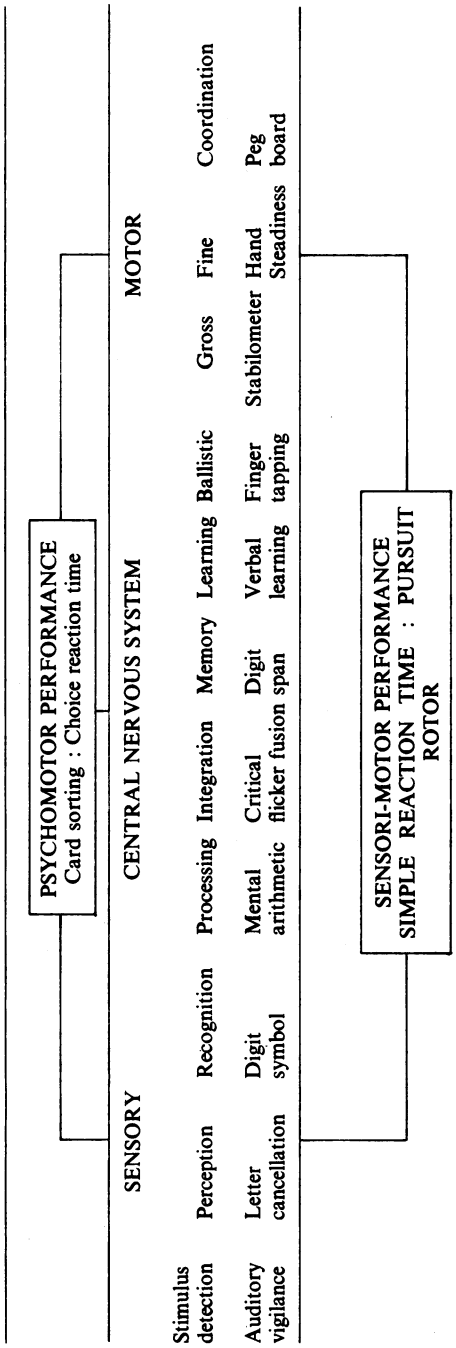
Table 3 Simple reaction time as a measure of psychoactive drug activity

Studies which have shown an impairment of reaction time following psychoactive medication		
Meprobamate	800mg	Huffman *et al.* (1963)
	1600mg	Kornetsky (1958); Uhr *et al.* (1963)
Butobarbitone	200mg	Walters & Lader (1971)
Amylobarbitone	100mg	Hart *et al.* (1976)
Nitrazepam	5 and 10mg	Peck *et al.* (1977)
Flurazepam	15 and 30mg	Bond & Lader (1973)
Flunitrazepam	1 and 2mg	Bond & Lader (1975)
Lorazepam	1.0mg	Hedges *et al.* (1971)
	2.0mg	Hedges *et al.* (1971), Harry & Richards (1972)
	2.5mg	File & Bond (1979)
	4.0mg	Harry & Richards (1972)
Diazepam	2.5mg	Hart *et al.* (1976)
	5mg	Hedges *et al.* (1971); Hart *et al.* (1976); Uhlenhuth *et al.* (1977)
	17–28mg	Shira (1978)
	20mg	Harry & Richards (1972)
Amitriptyline	25mg	Peck *et al.* (1979); Crome & Newman (1978)
Mianserin	20mg	Crome & Newman (1978)
Studies which have shown an improvement of reaction time following drug treatment		
Nicotine	2.0mg	Frankenhaeuser *et al.* (1970)
	2.2mg	Myrsten *et al.* (1971)
Nomifensine	100mg	Hindmarch (1977a)
Amphetamine	15mg	Taeuber *et al.* (1979)

Table 4 The choice reaction time (CRT) task and the action of some psychotropic substances

Studies where a decrement in CRT performance has followed psychoactive medication		
Amylobarbitone	100mg	Broadhurst & Arenillas (1975)
Dichloralphenazone	1300mg	Hindmarch *et al.* (1977b)
Meperidine	75mg	Korttila & Linnoila (1975)
Diphenhydramine	100mg	Moser *et al.* (1978)
Flurazepam	15mg	Broadhurst & Arenillas (1975)
	30mg	Church & Johnson (1979)
Nitrazepam	5mg	Hindmarch (1979a)
	10mg	Liljequist & Mattila (1979); Hindmarch & Clyde (1980b)
Temazepam	30mg	Hindmarch (1975, 1976b, 1979c)
Bromazepam	1.5mg	Richter & Hobi (1976)
	6.0mg	Saario (1976)
Lorazepam	2.0mg	Ogle *et al.* (1976)
Chlordiazepoxide	10mg	Hindmarch (1979a)
Diazepam	5mg	Ogle *et al.* (1976); Hindmarch (1979a)
	0.3mg/kg i.v.	Korttila *et al.* (1976)
	10mg	Korttila & Linnoila (1975); Mattila *et al.* (1978)
Amitriptyline + chlordiazepoxide	25mg + 10mg	Hindmarch *et al.* (1980)
Mianserin + alcohol	10mg + 0.5g/kg	Seppälä (1977)
Mianserin	10mg	Seppälä (1977)
Studies where an improvement in CRT performance has followed psychoactive medication		
Clobazam	10mg	Hindmarch (1979a)
Nomifensine	25mg	Hindmarch *et al.* (1980)

Table 5 A summary of tests of psychomotor function which have been shown to be sensitive to a wide range of psychoactive drugs



and Malpas (1972) found with nitrazepam 10 mg impaired card sorting time and Veldkamp *et al.* (1974) found triazolam 0.5 and 1.0 mg adversely affected card sorting performance. Berry *et al.* (1965) showed the sorting technique to be sensitive to changes in information processing brought about by three sub-anaesthetic doses of nitrous oxide and Haffner *et al.* (1973) have shown coloured card sorting to be impaired by ethanol 1.22 ml/kg and diazepam 10 and 20 mg. The card sorting technique as described by Berry *et al.* (1965), is a useful measure of sensori-motor performance which has been shown to be sensitive to a wide range of drugs. It has the added advantage, relative to other equipment based assessments, of being cheap and easy to score and administer.

Perhaps the most popular measure of sensori-motor performance is reaction time to a critical stimulus. Response or reaction time features in many assessments but it is useful to distinguish two varieties, *viz.* simple and complex, or choice, reaction time. The theoretical basis for both measures and valuable methodological comments are to be found in Teichner & Krebs (1972, 1974).

Simple reaction time involves a motor response, say button press, to an expected stimulus in the visual or auditory modality. The latency of the response is the reaction time. A choice reaction time is also a measure of the latency of a motor response but the critical stimulus is one of a number of alternatives and performance in the choice situation is, therefore, more dependant upon attentional monitoring abilities than it is in the simple response situation.

Table 3 presents details of simple reaction time findings and Table 4 presents studies where complex reaction time has been used.

It is clear from Tables 3 and 4 that reaction time is a sensitive measure of drug induced changes in sensori-motor performance. However, it is important to control for variability in motor response characteristics, i.e. the distance moved by the finger, arm or foot in making the response must be constant.

We have found it convenient to arrange the response buttons of a choice reaction time task about the arc of a circle and equidistant from a start button (Hindmarch & Parrott, 1978). Using this arrangement it is possible to measure three components of reaction time *viz.* the total reaction time from stimulus onset to completion of response, the movement time between start and response buttons and the processing time, obtained by subtracting the motor from the total reaction times.

The reaction time assessment whether it be simple or complex is only of use in psychopharmacological assessments of performance if the subject has received sufficient pre-test training to eliminate practice and learning effects. Under circumstances where subjects are at a performance plateau before they enter the

study, the reaction time measure can be used to discriminate drugs along a psychostimulant-sedative continuum.

The assessment of psychomotor function following the administration of psychoactive drugs

Psychoactive drugs act upon the mood, feelings and states of awareness of subjects or patients receiving them. The clinician has little to assess the course of drug action other than the verbal reports of patients receiving the treatment. Subjective reports of drug action on performance are valuable and sensitive to drug induced changes providing they are collected and collated in a meaningful and controlled manner.

The literature is replete with scales for the measurement of mood, depression, anxiety and affect. However, the majority of published scales are to aid diagnosis in a clinical situation and many of the questionnaires have low test/re-test reliability. As subjective awareness of drug activity is an important determinant of behavioural response it is necessary to discuss reliable ways of evaluating the activity of psychotropics on an individual's feelings.

Aitken (1969) produced strong arguments in favour of a 10 cm line visual analogue scale based on the earlier work of Freyd (1923) and Hayes & Patterson (1921) and Bond & Lader (1974) demonstrated the usefulness of line analogue rating scales in drug evaluation studies. Luria (1975) has reported the validity and reliability of visual analogue mood scales in psychiatric populations and Oswald, Lewis, Dunleavy, Brezinova & Briggs (1971) and Hindmarch (1975, 1976b, 1977b) the usefulness in measuring the integrity of early morning performance following the nocturnal administration of hypnotics. Březinová (1974) demonstrated the sensitivity of visual analogue scales to the stimulant effects of caffeine 300 mg and Hindmarch & Gudgeon (1980) have shown a differentiation of lorazepam and clobazam on line analogue ratings of alertness. The line analogue scale remains a useful index of drug activity, which can be tailored to the experimental goals of a particular study by choosing the bipolar qualifiers carefully.

The labels at the ends of the line must be semantic opposites. Useful lists of dimensions upon which to rate mood are to be found in Bond & Lader (1974), Hindmarch & Gudgeon (1980) and Hindmarch & Clyde (1980a, b). Visual analogue rating scales should be included in all studies of psychoactive drug activity along with a selection of the tests presented above. It is best to adopt a multi-assessment approach using one or more tests for each component part of psychomotor performance to maximise the detection of the effects of a psychoactive drug.

A scheme for conducting an investigation of the effects of a psychoactive drug on human psychomotor function is given below (Table 5), after a consideration of the tests and assessments reviewed above.

Any study which utilises measures from each of the above divisions of human psychomotor performance will produce relevant, valid and reliable results only if the experimental conditions, methodology and selection of subjects are carefully controlled.

On the completion of a study the effects observed, statistically significant or not, must be treated with caution as they are limited by the sensitivity of the assessments employed and the experimental sets operating in the particular instance. More credibility can be given to results which fit the findings of other researchers and complement the corpus of knowledge relating to a particular drug but adverse effects do not necessarily mean a drug is of no clinical value. Nicholson (1976) summarises the difficulties in interpreting data from performance studies but also indicates the relevance of performance studies both to psychopharmacology and to clinical practice. Although there are no simple answers to the questions generated by performance studies it is clear that only by carefully controlled experimentation will the effects of psychoactive drugs on psychomotor function be elucidated.

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