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Experimental Approaches To Psychiatric Diagnosis

Psychometric, Conditioning, and Psychopharmacological Studies

EXPERIMENTAL APPROACHES TO PSYCHIATRIC DIAGNOSIS

Psychometric, Conditioning, and Psychopharmacological Studies

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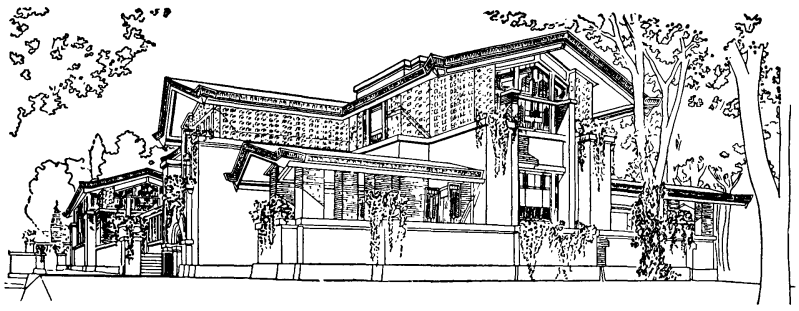

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PREFACE

New scientific disciplines usually appear at times of transition from the simpler forms of organization of matter to the more complex and thus not only incorporate the laws of scientific approaches dealing with simpler forms of conceptualization, but also develop their own rules of procedure, which usually transcend the laws of the parent disciplines.

This monograph is based on experiments which were carried out by the staff of the Research Department of the Douglas Hospital from 1962 to 1968. The studies were not uniform in design, quality, or sophistication, but all of them had one aim—that of differentiating psychiatric patients into groups on a different organizational level. However, the primary purpose of this monograph is not to present experimental results, but rather to demonstrate again the well-known phenomenon that the introduction of a new method often brings about new findings, or, in other terms, that advancement in a scientific discipline depends to an important degree upon methodological progress.

The experimental work discussed in these studies was supported by grants received from the following organizations: Public Health Service Research Grant MH-05202 and MH-08060, U. S. Department of Health, Education, and Welfare (1962–1968 and 1963–1968); Medical Research Council of Canada Grant MA-1936 (1967–1968); and Federal-Provincial Mental Health Grant 604-7-650 (1966–1967 and 1968–1969).

Many people—far more than can be mentioned by name—assisted in the preparation of this monograph. To all of them the authors owe thanks.

We are especially indebted to our Research Fellows and Residents during this period; namely, Doctors J. V. Ananth, S. M. Choi, Z. Cuculic, S. Debow, H. Edwards, S. Haraszty, S. Hattan-

gadi, L. Ho-Sze-Key, H. Siede, and D. Silver, for their conscientious co-ordination of the various studies. We are also obliged to the psychologists who participated in these studies. Without the untiring effort of Evelyn Adamo, M. Donald, A. A. Green, Hillary Lee, A. Lidsky, G. Nemeth, and B. M. Saxena, our data would never have been collected nor processed.

To all members of the Research Department of the Douglas Hospital we express our sincere appreciation for their collaboration throughout the six years when the material for this monograph was collected.

We are particularly grateful to Doctor W. Horsley Gantt, without whose encouragement this monograph would probably not have been written.

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EXPERIMENTAL APPROACHES TO PSYCHIATRIC DIAGNOSIS

Psychometric, Conditioning, and Psychopharmacological Studies

Chapter I

EXPERIMENTAL APPROACHES TO GERIATRIC DIAGNOSIS

It was only at the turn of the century that psychology was recognized as a descriptive science, with the implication that psychological functioning could never be completely understood by "explanatory methods" alone. With the emergence of scientific psychology the systematic study of human behavior began. The aims of scientific psychology, to establish general rules and laws of psychic functioning, were distinct from that of interpretive and empathic ("understanding") psychology.

In scientific psychology it is legitimate to hypothesize a causal connection between two events when they are found to follow each other frequently in a given temporal order. This probability, however, needs to be verified by a direct inquiry prior to being accepted as a scientifically established fact. In this frame of reference the introduction of a new method is the prerequisite of scientific progress.

This became obvious to us after completing the evaluation of a long-term research project which aimed at the prediction of therapeutic responsiveness to specific drugs in hospitalized geriatric patients. Since prediction can only be properly applied to classes of individuals who are, within limits, homogeneous with respect to a set of characteristics, our first efforts were directed towards finding methods which could effectively identify homogeneous classes of individuals within the geriatric patient population included in the clinical investigation. To achieve this aim we attempted to classify our patients according to nosological entity or diagnosis, characteristic psychopathology (as determined by typical symptom clusters), performance on a battery of seven psychometric tests and changes in test performance following specific "pharmacological loads." This primary homogenizing phase of our study was followed by the treatment phase of the investigation during which each patient was given six prototype drugs—

a psychostimulant (methylphenidate), an anxiolytic (meprobamate), an antidepressant (amitriptyline), an antipsychotic (thioridazine), a vitamin with vasodilator properties (nicotinic acid), and a steroid hormone (fluoxymesterone)—over an eight- to twelve-week period with a minimum of two weeks of drug-free intervals between them. Finally, we attempted to identify which of the diagnostic differentiations—the nosological, the psychopathological, the psychometric, or the psychopharmacological—would be the most meaningful for the prediction of general or more specific therapeutic drug effects.

Our experimental population consisted of 107 geriatric patients, residents in a mental hospital, which we divided into three clinical categories according to their *nosological* diagnoses: organic brain disease (38 patients), paranoid schizophrenia (27 patients), and nonparanoid schizophrenia (42 patients). The average age of this experimental sample was approximately seventy-one years and it did not differ significantly for any of the three main clinical nosological categories. The average length of hospital stay, however, was different among the three groups, i.e. it was seventeen years for patients with organic brain disease, twenty-one years for the paranoid, and twenty-eight years for the nonparanoid schizophrenics.

In the classification based on *psychopathological* manifestations, a modification of the Verdun Target Symptom Rating Scale was used (Table I). The modified scale referred to five symptom clusters: arousal, mood, mental integration, affect, and organicity. Under the heading "arousal," three symptoms were rated on a four-step scale: irritability, excitement, and fatigue; under the heading "affect," nine symptoms were rated: hostility, suspiciousness, anxiety, autonomic reactions, impulsiveness, compulsiveness, somatization, relational ability, and preoccupation with self; under the heading "mood," two symptoms were rated: depression and elation; under the heading "mental integration," three symptoms were rated: perceptual disturbance, thought disorder, and delusions; and under the heading "organicity," three symptoms were rated: memory disturbance, alteration of consciousness, and dementia.

For the purpose of *psychometric* differentiation, a short battery

TABLE I
MODIFIED VERDUN TARGET SYMPTOM RATING SCALE

Arousal	*Mood*
Irritability	Depression
Excitement	Elation
Fatiguability	*Mental Integration*
Affectivity	Perceptual disturbance
Hostility	Thought disorder
Suspiciousness	Delusion
Anxiety	*Organicity*
Autonomic reaction	Memory disturbance
Impulsiveness	Consciousness alteration
Compulsiveness	Dementia
Somatization	
Relational ability	
Preoccupation with self	

Each of the 20 items is scored from 0 to 3: 0 = absent; 1 = mild; 2 = moderate; 3 = marked.

of tests was devised. Since we were dealing with geriatric patients most of whom had a short attention and memory span, were easily fatigued, and not always cooperative, we were limited in the choice of psychometric tests which we could apply. We thought, however, that with a simple test battery we would be able to obtain some information on the four basic functions which might be considered fundamental requirements for any simple model of mental processes, i.e. input, output, information processing, and information storage-retrieval. As a result of these considerations our final test battery consisted of seven tests. Two of these tests were aimed at simple psychomotor functions: tapping speed and simple auditory reaction time. One test measured a perceptual function: critical flicker fusion frequency. One test measured associational functions: word association time. Three tests evaluated attention and short span memory: digit span forward and backward and a counting test which required the patient to count up to a number at which he had previosuly been instructed to stop.

For the *psychopharmacologically* based diagnostic classification four pharmacological loadings were used: a placebo (intravenous injection of normal saline), a psychostimulant (intravenous injec-

tion of methamphetamine, 10 mg), a central nervous system depressant (intravenous injection of sodium amobarbital, 250 mg) and a cerebral vasodilator (a five-minute inhalation of a 5 per cent carbon dioxide and 95 per cent oxygen mixture). Using the seven procedures of our psychometric test battery, all subjects were tested immediately before and within fifteen minutes after each pharmacological loading. Each subject was tested once under each of these four conditions on four different days, separated by at least one week.

All behavioral findings were evaluated clinically and all quantitative data were tested statistically. To our surprise, no clear differentiation of the three diagnostic groups could be made on the basis of the *psychopathological rating scale* assessments. A simple analysis of variance on the scores of the symptom clusters of the modified Verdun Target Symptom Rating Scale, comparing the three diagnostic categories of our patient population, yielded no significant differences of the "F" ratios. Thus, the probability of differentiating between the three patient groups of organic brain disease, paranoid schizophrenia, and nonparanoid schizophrenia on the basis of behavioral rating scale scores was low.[1]

Similarly, a simple analysis of variance performed on the performance scores of the patients in the three diagnostic categories on each *psychometric test* did not result in significant "F" ratios. However, when the mean performance on each psychological test was ranked across the groups it was found that patients with organic brain disease had the lowest scores on five out of the seven tests, i.e. reaction time, critical flicker fusion frequency, counting test, word association time, and digit span backward. This means that they did poorly in all three psychometric test categories, i.e. the afferent-perceptual, the central-cognitive, and

[1] This finding is in accordance with the clinical experience that it is often difficult to differentiate terminal phases of a functional psychosis from the manifestations of an organic brain disease. The difficulty is probably, partly, due to the fact that the clinical manifestations of a chronic psychosis frequently lose the incisive characteristics of their acute stages so that diagnostic differences between various chronic psychiatric disorders become blurred. Partly it may also be due to the fact that many schizophrenic patients who have grown old in a mental hospital have developed signs and symptoms of organic brain disease which have become superimposed on their functional symptomatology.

the efferent-psychomotor tests. On the other hand, paranoid patients scored highest on five of the seven tests, i.e. reaction time, counting test, word association time, and digit span forward and backward. A Friedman two-way analysis of variance by ranks of these results yielded a chi-square of 6.00. For a df equaling 2 this is significant at the 0.05 level of confidence.[2]

Finally, while neither the placebo, the methamphetamine, nor the carbon dioxide *loads* produced significant changes of the patient's performance on the psychometric test battery, under the influence of sodium amobarbital a statistically significant decrease in test performance was seen in all three diagnostic categories. When the data were analyzed further, it could be shown that the impaired functioning could be differentiated in that patients with organic brain disease showed a significant performance decrement on the efferent psychomotor tests (tapping speed and reaction time), the nonparanoid schizophrenics on the afferent perceptual test (critical flicker fusion frequency), and the paranoid schizophrenics on two of the central cognitive tests (digit span forward and backward).

Studying the relationships between all pretreatment assessment variables—that is, nosological, psychopathological, psychometric, psychopharmacological, and therapeutic outcome—involved the analysis of 414 possible associations. Of these, statistical analysis on the basis of contingency tables revealed only fifteen significant associations. Of these, three associations were significant at the 0.01, two at the 0.02, and ten on 0.05 levels of confidence.[3] According to these findings meprobamate treatment would be indicated for male patients with a high score on hostility, compulsiveness, and delusions, whose performance on the digit span forward test decreases under the influence of an amobarbital load. On the other hand patients who respond best to nicotinic acid were the ones characterized by a high score on thought disorder and a low

[2] The highest scores on the critical flicker fusion frequency test were observed in patients belonging to the diagnostic group of nonparanoid schizophrenics.

[3] Since four of the correlations at the 1 per cent level, eight at the 2 per cent level, and twenty at the 5 per cent level of confidence might have occurred by chance, it is difficult to be sure that any of our findings—and if any, which—might be considered as valid.

score on depression and by lowered performance on the counting test, produced by both the methamphetamine and the amobarbital loads. Good therapeutic responses to fluoxymesterone are inversely related to the length of hospitalization of geriatric patients and positively correlated with improved performance on the word association test following methamphetamine loading, improved performance on the digit span backward test following carbon dioxide loading, and reduced performance on the digit span backward test following amobarbital loading. The contingency table also suggests that the presence of delusions is negatively correlated with the therapeutic response to methylphenidate treatment and, finally, that female geriatric patients are more likely to improve on thioridazine than male patients.

Furthermore, while statistically nonsignificant, it was our clinical impression, based on observation of the patients and inspection of the data, that responses to pharmacological loads may be useful in the prediction of therapeutic changes with specific psychotropic drugs. Thus, it was seen that a favorable therapeutic response to thioridazine was associated with an *overall* decrease in psychometric performance following the pharmacological loads of both carbon dioxide and methamphetamine; a favorable therapeutic response to fluoxymesterone may be indicated by an overall improvement of psychometric test performance following loadings with carbon dioxide and methamphetamine and an impaired test performance following amobarbital loading;[4] a favorable therapeutic response to nicotinic acid might be anticipated in patients who show an overall improvement of test performance following carbon dioxide inhalation but respond with impaired test performance to the administration of methamphetamine and amobarbital;[5] a favorable therapeutic response to methylphenidate was associated with a worsening of test performance follow-

[4] Our statistically significant findings suggest that improved performance on the word association time test following the methamphetamine load, improved performance on the digit span backward test following the carbon dioxide load, and impaired performance on the digit span backward test following the amobarbital load are correlated with a favorable clinical response to fluoxymesterone.

[5] Consistent with this observation, our statistical results point to a correlation of impaired performance on the counting test following methamphetamine and impairment on the same test following amobarbital in those patients who show a favorable response to nicotinic acid.

ing carbon dioxide inhalation; and finally, a favorable therapeutic response to meprobamate may be indicated by an improvement of test performance following carbon dioxide inhalation (and an unfavorable therapeutic response to meprobamate by impaired test performance after carbon dioxide inhalation).

As a result of our geriatric study it was recognized that the particular rating scale we used was ineffective in differentiating groups of patients taken from a chronically hospitalized population. On the other hand, our psychometric test battery yielded response patterns or profiles which could be correlated with nosological categories. Furthermore, the immediate drug-induced changes on the psychometric test battery, following specific pharmacological loads, were correlated with long-term therapeutic outcome to the administration of specific psychoactive drugs. Thus, the introduction of the psychometric method provided means for differentiating homogenous groups which corresponded with the traditional nosological categories and, the introduction of the psychopharmacological method made it possible to differentiate homogeneous groups which corresponded with the differential therapeutic responsiveness to psychoactive drugs.[6]

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Chapter II

PSYCHOMETRIC TESTS AND PSYCHIATRIC DIAGNOSIS

The psychometric correlates of psychopathology have been subjected to scientific inquiry since Kraepelin's (1896) first clinical application of different testing procedures developed by Wundt (1873) and elaborated in his laboratories. Important early contributions were made to the study of psychometric performance of psychiatric patients in the areas of perception (Bidwell, 1896) and psychomotor functioning (Hirsch, 1861; Obersteiner, 1874); association and learning (Galton, 1879; Trautscholdt, 1883; and Cattell, 1886); and pharmacologically induced performance changes (Kraepelin, 1883).[7]

Following the early experiments came five decades of experimental studies which amassed a great deal of information regarding the nature of psychometric performance changes in the different psychopathological conditions. The majority of studies were limited to the information which one particular test could reveal under different psychopathological conditions, or to the information which a number of tests could give in some specific psychopathology. The evaluation of multivariate investigations, as for example the early factor analytic studies of Stephenson (1935, 1936), Line and Griffin (1935), and Eysenck (1941) before the

[7] References: Kraepelin, E.: Der Psychologische Versuch in der Psychiatrie. *Psychol Arb, 1*:63, 1896; Wundt, W.: Principles of physiological psychology. New York, Macmillan, 1873; Bidwell, S.: On subjective color phenomenon attending sudden changes of illumination. *Proc Roy Soc, 60*:368, 1896; Hirsch, A.: Experiences chronoscopiques sur la vitesse des differentes sensations et de la transmission nerveuse. *Soc Sci Natl Bull, 6*:600, 1861; Obersteiner, H.: Ueber eine neue Einfache Methode zur Bestimmung der Psychischen Leistungsfaehigkeit des Gehirnes Geisteskranker. *Virchow Arch, 59*:427, 1874; Galton, F.: Psychometric experiments. *Brain, 2*:149, 1879; Trautscholdt, M.: Experimentelle Untersuchungen ueber die Association der Vorstellungen. *Philo, 571*:213, 1883; Cattell, J. McK.: Experiments on the association of ideas. *Mind, 12*:68, 1887; and Kraepelin, E.: Ueber die Einwirkung einiger medicamentoeser Stoffe auf die Dauer einfacher psychischer Vorgaenge. *Philos, 57(1)*:417, 1883.

advent of modern data processing entailed great difficulties.[8]

The development of new electronic instrumentation in neurophysiology threw new light on the physiology of central nervous system functions as measured by psychometric tests, and similarly the development of electronic computers allowed a more effective use of large-scale multivariate methods in studying the interrelationships of various functions. In this new era, created by technological progress, the establishment of psychometric correlates of the various clinical psychopathological syndromes became especially meaningful and timely.

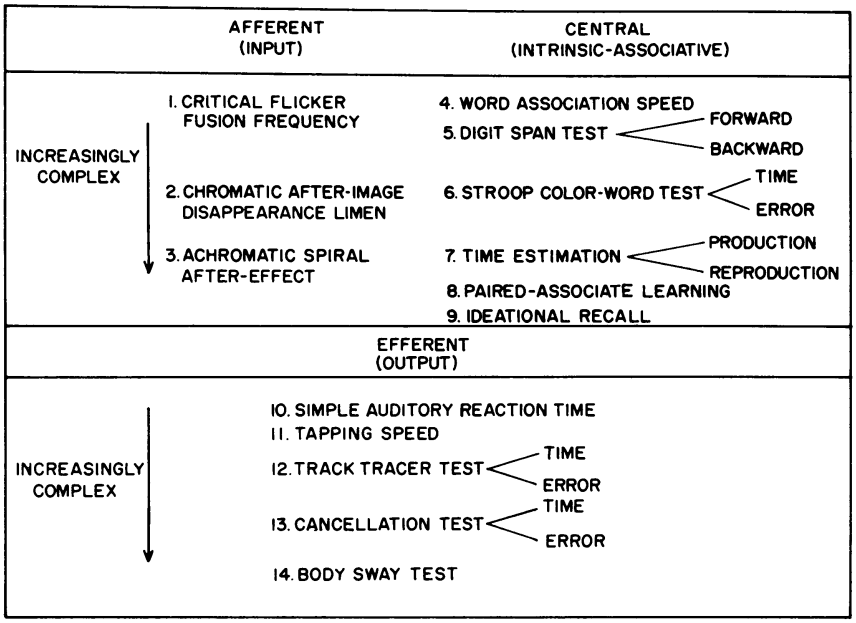
A PSYCHOMETRIC TEST BATTERY

For studying the psychometric correlates of psychiatric diagnosis we developed a battery of tests in the early sixties. The "battery" was the result of careful selection of tests with established value in the measurement of the different psychopathological syndromes present in the major psychiatric illnesses. Designed specifically for clinical use with mental hospital patients, it was developed with the knowledge that unmedicated acute patients are often irritable, destructive, or frightened by complex apparatus; that chronic patients are often too confused, incoherent, or demented to perform a complex task; and that both pathological groups are easily frustrated and fatigued and thus have a short attention span. Under all these conditions the tests had to be simple enough to be understood with minimal explanations, easy enough to be performed with minimal practice, and brief enough for the total battery to be administered within a relatively short period of time.

The selected tests were classified in accordance with the functions they measured (Table II). On this basis all the tests of the battery fell into three groups: tests of the first group measured

[8] References: Stephenson, W.: Correlating persons instead of tests. *Char pers, 4*:17, 1935; Stephenson, W.: The inverted factor technique. *J Psychol, 26*:344, 1936; Line, W., and Griffin, J. D. M.: Objective determination of factors underlying mental health. *Amer J Psychiat, 91*:833, 1935; and Eysenck, H. J.: "Type" factors in aesthetic judgements. *Brit J Psychol, 31*:262, 1941.

TABLE II
FOURTEEN TESTS OF THE PSYCHOMETRIC TEST BATTERY



primarily afferent functions, tests of the second group primarily central functions, and tests of the third group primarily efferent functions of the nervous system. Valid administration of this test battery requires a common set in each subject, to the effect that an ability to grasp simple verbal instructions and a certain minimal willingness to perform the tasks is assumed. In the absence of either of these, test results cannot be meaningfully evaluated.

In the following, the relevant information on the fourteen tests of this battery is briefly given.[9]

Afferent-Perceptual Tests

Critical Flicker Fusion Frequency (CFF)

The first experimental work, in which the "flicker fusion frequency" phenomenon was studied, was carried out by Talbot

[9] In the collection of background information on the various tests W. Noe, B.A., was of assistance.

(1843). The apparatus he used consisted of a light source which was viewed by the experimental subject through a sector of a rotating disk. The subject reported on seeing a flickering light at low frequency rotation of the disk which then was fused into a steady light stimulus as the rate of rotation was increased. The frequency of rotation at which the subject no longer perceived flicker was called his CFF threshold. In more recent studies the "rotating sector disk" has been replaced by a neon light source whose rate of flicker is electronically controlled (Aiba, 1963).[10]

The variables of the CFF phenomenon have been elaborated and described by Ross (1936, 1936, 1938) and Landis (1951, 1953, 1954). The CFF was considered as a method for measuring the temporal discriminatory power of the visual system by Osgood (1953) and, as a result of factor analytic studies, Halstead (1947) suggested that it is a component of the "power factor" of biological intelligence.[11]

In the procedure employed in our studies the subject is seated facing the apparatus, a test patch three-fourths of an inch in diameter, at a distance of three feet (at eye level). An electronically controlled intermittent neon light (5 watt) is manually adjusted from low (20) to high (80) frequency oscillations until the flicker fusion threshold is reached. The raw score is expressed in cycles per second, and the mean score computed on the basis of three trials.

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[10] References: Talbot, H. F.: Experiments on light. *Phil Mag, 13*:321, 1834; and Aiba, S.: The suppression of the primary visual stimulus. In Eysenck, H. J. (Ed.): *Experiments with Drugs.* New York, Pergamon Press, 1963.

[11] References: Ross, R. D.: A comparison of the regional ingredient of fusion frequency and visual acuity. *Psychol Mono, 47*:306, 1936; Ross, R. D.: The fusion frequency in different areas of the visual field. I. The foveal fusion frequency. *J Gen Psychol, 15*:133, 1936; Ross, R. D.: The fusion frequency in different areas of the visual field. III. Foveal fusion frequency as a function of the light-dark ratio for constant retinal illumination at fusion. *J Gen Psychol, 18*:111, 1938; Landis, C.: Something about flicker fusion. *Scientific Mono, 3*:308, 1951; Landis, C.: An annotated bibliography of flicker fusion phenomenon. The Armed Forces National Research Council, Michigan, 1953; Landis, C.: Determinants of the critical flicker fusion threshold. *Physiol Rev, 34*:259, 1954; Osgood, C. E.: Method and theory in experimental psychopathology. New York, Oxford University Press, 1953; and Halstead, W. C.: Brain and intelligence. A quantitative study of the frontal lobes. Chicago, University of Chicago Press, 1947.

Chromatic After-Image Disappearance Limen (AID)

The chromatic after-image phenomenon was first demonstrated by Bidwell (1896, 1897). His instrument consisted of a disk, which was painted half white and half black, with a twenty degrees sector cut from it along the dividing line, in front of a red light source. Rotation of the disk under sufficient illumination interfered with the perception of this red stimulus. Instead its negative green after-image was seen. Lehmann (1950) placed Polaroid density filters in front of the aperture of the machine to allow a gradual control of the illumination level. He called the level of illumination at which the subject no longer saw any green in the stimulus the "after-image disappearance threshold."[12]

In the procedure employed in our studies the subject is seated facing the apparatus at a distance of three feet at eye level. The disk is rotated at 300 revolutions per minute in front of a 25-watt red light. A moveable Polaroid glass filter, or an optical neutral grey wedge, is gradually adjusted to decrease the level of illumination to the point where the subject sees only the red stimulus. The raw score is expressed in numbers on an arbitrary filter density scale from 0 to 100 and the mean score is computed on the basis of three trials.

Achromatic Spiral After-Effect (SPIR)

The achromatic spiral after-effect phenomenon was first described by Plateau (1835). He noted that a disk with an Archimedes spiral painted upon it appears to be expanding as it rotates clockwise and appears to be contracting as it rotates counterclockwise. Furthermore, Plateau recognized also that after the movement of the disk has been observed for some time, a reversed motion is perceived after discontinuation of the rotation.[13]

In the procedure employed in our studies the subject is seated

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[12] References: Bidwell, S.: On subjective color phenomenon attending sudden changes of illumination. *Proc Roy Soc, 60*:368, 1896; Bidwell, S.: On negative after-images following brief retinal excitation. *Proc Roy Soc, 61*:268, 1897; and Lehmann, H. E.: Preliminary report on a device for the objective measurement of the negative after-image phenomenon. *Science,* 112:199, 1950.

[13] References: Plateau, J.: Betrachtungen über ein von Hrn. Talbot vorgeschlagenes photometrisches Princip. *Ann Physik Chem, 35*:457, 1835.

facing an Archimedes spiral ten inches in diameter, painted black on a white disk, at a distance of three feet at eye level. The disk is rotated at 100 revolutions per minute for twenty seconds and then stopped suddenly. The raw score is expressed as 0 (i.e. achromatic after-effect not present) or 1 (i.e. achromatic after-effect present) and the mean score is computed on the basis of two trials (one clockwise and one counterclockwise).

Central-Intrinsic Tests

Word Association Speed (WAS)

The first experimental work in which word association speed was studied was done by Galton (1879, 1883). Using a list of seventy-five stimulus words, arranged in an order unknown to himself, he measured the time elapsed between his self-presentation of these stimulus words and his first expressed association. The variables of the word association speed test were extensively studied by many others, notably Jung (1918), and a standardization of this test was carried out by Kent and Rosanoff (1910).[14]

In the procedure employed in our studies the experimental subject is asked to express his first verbal association to each word from a list of ten common words drawn from the Kent-Rosanoff word frequency tables. The list of words is as follows: table, dark, slow, dog, bitter, heavy, carpet, ink, high, and black. The examiner reads each word out loud and records the subject's first response time to each of them. The raw score is expressed in 100's of a second, and the mean score is calculated on the basis of the responses to each of the ten words.

Digits Span Test—Forward (DF), Backward (DB), and Total (DT)

The repetition of a series of digits presented (usually read out loud) by an examiner was first used in the classical memory ex-

[14] References: Galton, F.: Psychometric experiments. *Brain, 2*:149, 1879; Galton, F.: Enquiries into human faculty and its development. London, Macmillan, 1883; Jung, C. G.: Studies in word association. London, William Heinemann, 1918; and Kent, G. H., and Rosanoff, A. J.: The study of association in insanity. *Amer J Insan, 68*:317, 1910.