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Utility of a computerized, *paced* semantic verbal fluency paradigm in differentiating schizophrenia and healthy subjects

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ABSTRACT

Functional magnetic resonance imaging (fMRI) paradigms designed to study word generation traditionally utilize a computerized *paced* version of the verbal fluency task (VFT) comprising 'blocks' of word generation and a baseline word repetition task. The utility of the above *paced* VFT paradigm in differentiating neuropsychiatric patients from healthy subjects has not been systematically examined. We administered a computerized, *paced* version of the semantic VFT comprising word generation and word repetition blocks to 24 schizophrenia and 24 matched healthy subjects, both before and during fMRI acquisition. The performance of patients with schizophrenia was significantly inferior to that of healthy control subjects in both the 'pre-scan' and 'intra-scan' sessions of the computerized *paced* semantic VFT. Specifically, schizophrenia patients generated significantly fewer total responses (VFTR) as well as correct responses (VFCR), but a larger number of 'no response' trials. However, there were no significant group differences in perseverative responses in the pre-scan session or 'intra-scan' sessions. The above computerized task has been reported by us previously to generate a behavioral performance index with hemodynamic correlates (John et al., 2011). Thus, our findings support the use of computerized *paced* VFT comprising word generation and word repetition blocks in both clinical and research settings.

1. Introduction

Verbal fluency, or the capacity for word generation, has been used as a test of frontal and temporal lobe functioning in various neuropsychiatric conditions like fronto-temporal dementia (Rascovsky et al., 2007), Alzheimer's disease (Henry and Crawford, 2004; Rascovsky et al., 2007), Parkinson's disease (Henry and Crawford, 2004), Huntington's disease (Ho et al., 2002) and schizophrenia (Ojeda et al., 2008; Curtis et al., 1998). Frontal lobes are involved in initiation and retrieval of information, while the role of temporal lobes is more specific to semantic memory in verbal fluency (Rascovsky et al., 2007). Patients with frontal lesions, therefore, show deficits in both semantic and letter verbal fluency tasks (VFT) (Baldo et al., 2001). Verbal fluency paradigms require subjects to generate words in response to phonological (words beginning with a particular letter, e.g., F, A, S) or semantic (words belonging to a particular category, e.g., animals, birds, flowers) cues (Lezak, 1995). In conventional semantic VFT paradigms, the subject is asked to generate as many examples that belong to a specific category like animals, fruits, or objects, in a given period of time (one or two minutes).

With the advent of functional magnetic resonance imaging (fMRI) in the 1990s, verbal fluency paradigms were adapted to suit the image acquisition requirements during cognitive activation experiments. Since the *un-paced* responses in conventional paradigms posed problems for the detection of task-related blood oxygenation level dependent (BOLD) signals (Basho et al., 2007), fMRI paradigms used *paced* production of words for obtaining more robust activations. Paced production of words is characterized by superior error detection and greater inhibitory control associated with greater anterior cingulate activations, when compared to *un-paced* word generation (Frith et al., 1995; Fu et al., 2002; Basho et al., 2007). This could result in improved

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accuracy of responses as well as reduced number of perseverative responses with paced verbal fluency paradigms in comparison to *un-paced* paradigms. A study of the effects of generation mode in semantic fluency by Basho et al. (2007) concluded that the paced, overt adaptation of the conventional VFT is best suited for use in fMRI paradigms, owing to their superiority with regard to control over and monitoring of behavioral responses. Thus, there could be some merit in using the above computerized paced, overt adaptation of the conventional VFT even in clinical situations. Another advantage of the computerized version of the VFT is that the verbal responses of subjects can be recorded along with generating behavioral response parameters such as response latency, while this is not possible with the conventional VFT used in clinical situations. Moreover, audio-taping the responses reduces the dependence on the examiner's memory and writing speed for accurate scoring of correct, incorrect and perseverative responses (e.g., Chan et al., 2003).

Among psychiatric disorders, verbal fluency deficits have been most consistently demonstrated in patients with schizophrenia in behavioral (Ojeda et al., 2008) as well as fMRI (Curtis et al., 1998) experiments. Semantic verbal fluency has been shown to have higher discriminating power to elicit significantly larger group differences between individuals with schizophrenia and healthy controls than phonological fluency (Melinder et al., 2005). Semantic verbal fluency deficits, unlike phonemic and design fluency deficits, were found even in early onset schizophrenia patients (Phillips et al., 2004). Moreover, relatives of schizophrenia patients were also found to perform less well than controls on semantic and (to a lesser extent) phonemic verbal fluency (Szoke et al., 2005). Thus semantic verbal fluency has been suggested as the best candidate for cognitive endophenotype of schizophrenia (Phillips et al., 2004; Szoke et al., 2005). Using a semantic verbal fluency paradigm, we have recently reported that schizophrenia subjects showed aberrant fMRI BOLD activations and deficient deactivations during semantic word generation in comparison to matched healthy subjects (John et al., 2011).

Word generation paradigms optimized for fMRI experiments typically comprise at least two tasks – a word generation condition as well as a baseline condition (e.g., word repetition task) administered alternately in "blocks" using some stimulus presentation software. As mentioned above, the paced version of the VFT used in such experiments differs substantially from the conventional *un-paced* versions with respect to its underlying physiology and the cognitive processing. Despite VFT studies using such *paced* fMRI paradigms being in vogue since the early 90s (e.g., Hugdahl et al., 1999), no study has so far reported whether this computerized *paced*-overt version of the VFT comprising both word generation and baseline tasks could reliably differentiate schizophrenia from healthy subjects.

In the present paper, we report the utility of the computerized *paced* semantic verbal fluency paradigm that was used in the above-cited fMRI study (John et al., 2011) in differentiating schizophrenia and healthy subjects, both in the fMRI-experimental setting as well as outside the scanner, and highlight its potential advantages over conventional VFT paradigms. We compared the behavioral responses during the "intra-scan" session, of the same set of subjects who participated in the above fMRI study with that during the "pre-scan" session (i.e., following the pre-scan training) to examine the utility of the computerized *paced*, overt version of the VFT task in differentiating schizophrenia subjects from matched healthy comparison subjects. We hypothesized that the computerized *paced*, overt semantic VFT would discriminate schizophrenia subjects from matched healthy comparison subjects, both during the 'pre-scan' blocks as well as the 'intra-scan' blocks. We further hypothesized, based on a large number of previous studies (Curtis et al., 1998; Melinder et al., 2005; Szoke et al., 2005; Ojeda et al., 2008), that schizophrenia subjects would perform worse than healthy control subjects in both conditions.

2. Methods

The study was carried out at the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India, with due approval from the NIMHANS ethics committee, thus conforming to the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all subjects (and their legally qualified representatives in case of patients) prior to enrollment into the study.

2.1. Subjects

The study samples comprised of 24 healthy subjects (HS) (mean age = 27.42 years (*S.D.* = 6.27; 19 males) who were recruited by word of mouth and constituted predominantly by hospital staff and their contacts, as well as 24 schizophrenia patients (SZ) (mean age = 30.13 years (*S.D.* = 9.48; 16 males), recruited from the outpatient department of NIMHANS by purposive sampling. The socio-demographic and clinical characteristics of the study samples are detailed in John et al. (2011). Only right handed [as determined by modified Annett's inventory (Annett, 1976)] subjects in the age group of 17–50, with a Mini Mental Status Examination (MMSE) score of 23 or more were included in the study. All participants were native speakers of various South Indian Dravidian languages (Table 1) and could read their preferred language with ease. None of these subjects were formally exposed to a second language other than their mother tongue before age six. A study-specific questionnaire to assess the speaking, reading and writing skills in different languages as well as to ascertain the primary language was administered prior to recruiting the subjects for the fMRI experiment. The matrix reasoning module of Wechsler's Adult Intelligence Scale-III (WAIS-III) (Wechsler, 1997) was administered on all subjects to determine their perceptual organization ability. This provided an index of their intellectual ability, independent of verbal abilities. The samples were matched for age, education status, handedness, and WAIS-III scores. Group comparisons of age, WAIS-III scores, Hindi Mental State Exam (HMSE) scores, years of education and gender distribution are given in Table 1. There were no significant group differences on these variables.

The Diagnostic and Statistical Manual for Mental Disorders-Fourth Edition (DSM-IV) (American Psychiatric Association, 2000) was used to arrive at a diagnosis of schizophrenia or schizophreniform disorder based on the consensus of the research psychiatrist who conducted a semi-structured interview and a trained research assistant who administered the Mini International Neuropsychiatric Interview (MINI) Plus (Sheehan et al., 1998). Two trained raters with good inter-rater reliability evaluated the baseline severity of schizophrenia psychopathology using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The healthy comparison subjects were ascertained to be free from Axis I or II psychiatric disorders using the MINI-Plus (Sheehan et al., 1998). The presence of other medical/neurological conditions requiring continuous medications, current use of psychotropic drugs and history of psychiatric illness in first-degree relatives were ruled out by an unstructured clinical interview.

2.2. Computerized verbal fluency paradigm

The computerized *paced*, overt verbal fluency protocol comprised of two tasks, viz., the "word repetition" condition and the "semantic category word generation" condition (Supplementary