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Procedural learning in schizophrenia: a functional magnetic resonance imaging investigation

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Abstract

Procedural learning (PL) is a type of rule-based learning in which performance facilitation occurs with practice on task without the need for conscious awareness. Schizophrenic patients have often (though not invariably) been found to show impaired PL. We performed functional magnetic resonance imaging (fMRI) during a blocked, periodic sequence-learning task with groups of: (i) healthy subjects, and (ii) schizophrenic patients on conventional antipsychotics. Healthy subjects showed significant PL, but patients did not. In healthy subjects, PL was associated with increased activation in the striatum, thalamus, cerebellum, precuneus, medial frontal lobe, and cingulate gyrus. The power of activation in the thalamus, striatum, precuneus, cingulate gyrus and BA 6 was related to the magnitude of PL in these subjects. No regions, except the anterior inferior gyrus, were significantly activated in patients. The caudate nucleus, thalamus, precuneus, and sensorimotor regions were activated significantly differently between the two groups. The findings demonstrate the involvement of the striatum, cerebellum, thalamus, cingulate gyrus, precuneus, and sensorimotor regions in PL. Further fMRI studies of PL in normal subjects treated with conventional antipsychotics, drug naïve patients, and patients given atypical antipsychotics would help to clarify the roles of schizophrenic disease processes and antipsychotic medication in impaired PL and associated brain abnormalities in schizophrenia.

Keywords: Procedural learning; Striatum; Cerebellum; Functional magnetic resonance imaging; Schizophrenia; Antipsychotics

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1. Introduction

Procedural learning (PL) is a form of skill acquisition in which learning occurs as a function of practice on task, without the need for conscious awareness of the learned skill or routine (Cohen and Squire, 1980; Squire and Zola-Morgan, 1988). In normal subjects, PL is found to be independent of intelligence (Feldman et al., 1995) and also of performance on tests of declarative learning and memory, such as recall or recognition in which performance depends on the knowledge of facts and often correlates with intelligence (Feldman et al., 1995). In clinical populations such as patients with Huntington's disease or cerebellar disorder, PL deficits are not predicted by global cognitive impairment or performance on tests of declarative memory function (Doyon et al., 1997). Supporting further the autonomy between PL and declarative memory systems, patients with amnesia show normal PL, but impaired declarative memory (Cohen and Squire, 1980).

The functional neuroanatomy of PL has not been fully established using functional resonance magnetic imaging (fMRI). The brain structures thought to have important roles to play in PL are the basal ganglia, in particular the striatum, and the cerebellum (Doyon et al., 1997; Grafton et al., 1995; Heindel et al., 1989; Hikosaka et al., 1999; Knopman and Nissen, 1991; Knowlton et al., 1996; Pascual-Leone et al., 1993). The evidence for the involvement of basal ganglia, striatum and cerebellum is provided by the observations of impaired PL using variants of the serial reaction time task (SRT; involves learning of sequences) in patients with Parkinson's disease (Doyon et al., 1997; Pascual-Leone et al., 1993), Huntington's disease (Knopman and Nissen, 1991; Willingham et al., 1996) and with damage to the cerebellum (Doyon et al., 1997; Gomez-Beldarrain et al., 1998; Molinari et al., 1997; Pascual-Leone et al., 1993).

The frontal cortex has also been proposed (Seger, 1994) and shown to be an important component of the circuit subserving PL (Jenkins et al., 1994; Doyon et al., 1996; Honda et al., 1998); both the striatum (Alexander and Crutcher, 1990) and the cerebellum (Schmahmann, 1991) project to the frontal lobe via the thalamus. Patients with prefrontal lesions show impaired PL on the SRT (Gomez-Beldarrain et al., 1999). An association between rapid skill acquisition on the pursuit rotor task and regional cerebral blood flow, assessed using positron emission tomography (PET), in premotor, prefrontal and cingulate regions has also been found (Grafton et al., 1994).

We investigated the neural correlates of PL in healthy subjects and schizophrenic patients using whole brain fMRI and a relatively simple non-verbal task. There have been previous attempts to investigate PL in schizophrenia. One difficulty, however, in evaluating PL performance in schizophrenia is that previous studies have measured it with different tasks (review, Green et al., 1997). In general, there are more studies reporting intact PL (Clare et al., 1993; Goldberg et al., 1993; Granholm et al., 1993) than those reporting impaired PL using the pursuit rotor task (Schwartz et al., 1996) in this population. Studies using the Tower of Hanoi have shown that patients initially have difficulty on this task and may not show the same rate of improvements as seen in healthy subjects (Goldberg et al., 1990). PL, as indexed by mirror drawing performance, has been found to be relatively intact in drug-naïve and clozapine-treated patients, compared to those treated with conventional antipsychotic drugs (Bedard et al., 1996, 2000). The learning of sequences on the SRT has been found to be impaired in schizophrenic patients (Green et al., 1997; Kern et al., 1998). The neuroanatomical or neurochemical basis of impaired PL in schizophrenia is not clear. Differences in the results of studies of PL in schizophrenia may be due to the measure of PL employed. The tasks differ considerably in terms of inherent complexity and the involvement of motoric and cognitive processes. Thus, they are likely to differ also in the involvement of specific brain regions in the execution and/or their sensitivity to pharmacological treatments.

This study, to our knowledge, is the first to explore the neural correlates of PL in schizophrenia. Based on previous studies in clinical populations and PET studies in normal subjects (see above), the striatum (mainly caudate nucleus), thalamus, cerebellum and frontal regions were expected to be activated in association with PL in normal subjects. Patients were hypothesized to show impaired PL and, if so, a lack of or altered activation in regions associated with PL in healthy subjects.

2. Methods

2.1. Subjects

Six healthy subjects and six patients with schizophrenia (all right handed, males) participated as subjects. Healthy subjects (mean age = 31.83 years, SD = 4.88) were screened for a history of mental illness, anorexia, drug and alcohol abuse, regular medical prescription, and presence of psychosis in their first-degree relatives via a semi-structured interview. Patients (mean age = 34.67 years, SD = 4.41) were diagnosed as having paranoid schizophrenia by a psychiatrist using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995). Four patients were Caucasian and two were Afro-Caribbean. One patient had a past history of alcohol and substance abuse, but all patients were free from alcohol and substance abuse for at least 1 year prior to taking part in this study. Only one patient was on regular anticholinergic medication (procyclidine, 10 mg/daily). No patient scored more than 0 on the Barnes Akathisia Scale (Barnes, 1989). On average, they had 13 years of education and had been ill for 10.5 years (range: 2–19 years). Their symptoms were rated using the positive and negative syndrome scale (PANSS) (Kay et al., 1987; mean positive symptoms = 9.50, SD = 4.18; negative symptoms = 11.33, 3.67; general psychopathology = 22.50, 6.19). All patients were on conventional antipsychotics (mean medication dose as chlorpromazine equivalents = 410.17 mg, SD = 298.88) for at least 6 months prior to their fMRI scans.

The study was approved by the Institute of Psychiatry (Research) Ethical Committee. Written informed consent was obtained from all subjects after the experimental procedures had been explained to them.

2.2. Experimental design and procedure

All subjects performed a 5-min sequence learning task in a blocked periodic AB design; this was a modified version of the task used in our previous pharmacological study (Kumari et al., 1997) while undergoing fMRI. The task consisted of two 30-s alternating conditions: blocks of random trials (OFF, control condition) and blocks of pattern trials (ON, experimental condition). In total, there were five blocks of random trials and five blocks of pattern trials. Subjects were presented with a white target stimulus (an asterisk) on a black screen, viewed via a prismatic mirror fitted in the radiofrequency head coil, as they lay in the scanner. This target moved between four locations on the screen, which was divided into four equal quadrants by two intersecting white lines. The target movements during the pattern trials were predictable for 75% of cases, i.e. determined following three specific rules: (1) a horizontal target movement was followed by a vertical target movement; (2) a vertical target movement was followed by a diagonal target movement; (3) a diagonal target movement was followed by a horizontal movement. The fourth movement of the target during the pattern trials was unpredictable, which then was followed by the above mentioned three specific rules (see Fig. 1).

Subjects were not told of the existence of specific rules governing the target movements during the pattern blocks, and the beginning of random and pattern blocks was not marked in any way. Subjects were asked to follow each target movement with their right hand as fast as possible using an MR compatible key pad with four keys, each key corresponding to one of the four quadrants. The movement of the target was initiated by the subjects' touching the target key. Reaction times were recorded on-line.

Prior to scanning, all subjects underwent a practice session during which they practiced on five 30-s blocks of random trials and five 30-s blocks of pattern trials, both alternated with 30-s rest periods. It was felt that patients would require exposure to the task and the button pad prior to being exposed them in the scanner. The practice session was identical for both patients and healthy subjects.

2.3. Image acquisition

Echoplanar MR brain images were acquired using a 1.5-T GE Signa system (General Electric, Milwaukee WI, USA) fitted with Advanced NMR hardware and software (ANMR, Woburn MA, USA) at the Maudsley Hospital, London. Daily quality assurance was carried out to ensure high signal to ghost ratio, consistent high signal to noise ratio and excellent temporal stability using an automated quality control procedure (Simmons et al., 1999). A quadrature bird-

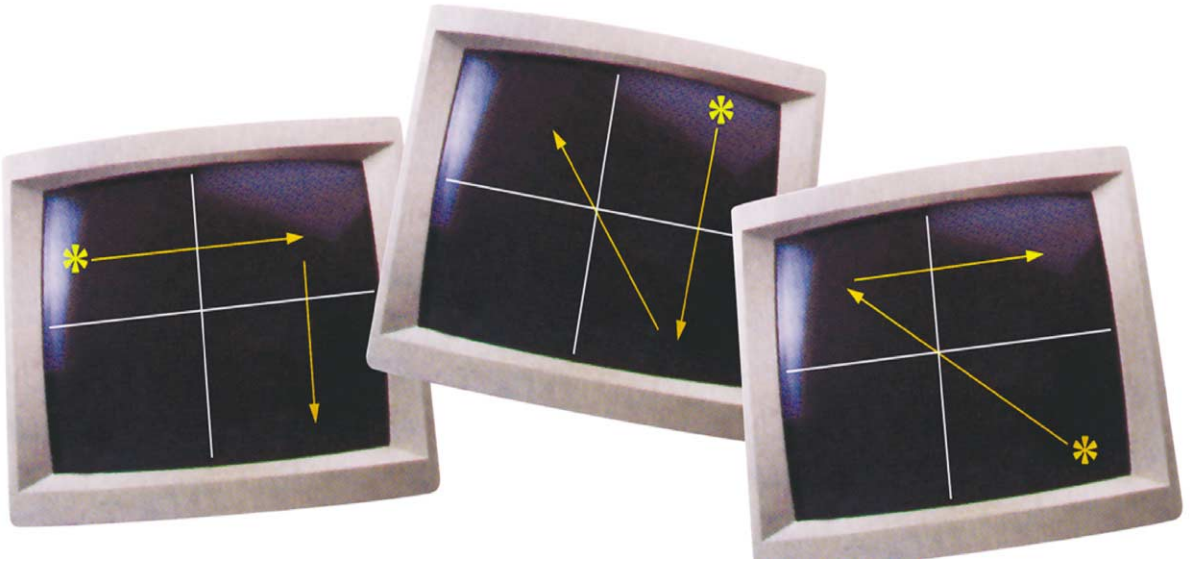

Fig. 1. An illustration of pattern trial rules.

cage head coil was used for RF transmission and reception. In each of 14 near-axial non-contiguous planes parallel to the inter-commissural (AC-PC) plane, 100 T_2*-weighted MR images depicting blood-oxygenation-level-dependent (BOLD) contrast (Ogawa et al., 1990) were acquired over the 5-min experiment with echo time (TE) = 40 ms, repetition time (TR) = 3 s, in-plane resolution = 3.1 mm, slice thickness = 7.0 mm, interslice gap = 0.7 mm. Head movement was limited by foam padding within the head coil and a restraining band across the forehead. In the same session, a 43-slice, high resolution inversion recovery echoplanar image of the whole brain was acquired in the AC-PC plane with TE = 80 ms, TI = 180 ms, TR = 16 s, in-plane resolution = 1.5 mm, slice thickness = 3.0 mm, interslice gap = 0.3 mm.

2.4. Data analyses

2.4.1. Behavioural measures

The difference between the mean reaction times to random and pattern trials represented the amount of PL. These data were analysed by a three-way Group (normal subjects, patients) × Trial Type (Random, Pattern) × Block (five 30-s blocks of Random and Pattern Trials) analysis of variance.

2.4.2. Image analysis

Following correction of movement related effects (Bullmore et al., 1999a), the power of periodic signal change at the (fundamental) OFF–ON frequency of stimulation was estimated by iterated least squares fitting a sinusoidal regression model to the time series at each voxel of all images. The fundamental power quotient (FPQ = sinusoidal power at fundamental frequency divided by its standard error) was estimated at each voxel and represented in a parametric map (Bullmore et al., 1996). After these power maps had been transformed to standard space (Talairach and Tournoux, 1988) and smoothed by a 2D Gaussian filter (FWHM = 7 mm), generic brain activation maps identifying intracerebral voxels with large median power of activation over all subjects in each group were constructed by a permutation test procedure (Brammer et al., 1997); voxel-wise one-tailed probability of type 1 error $p < 0.005$. Between-group differences in mean power of response were estimated at each voxel by fitting a one-way analysis of covariance model (with global power of response as a covariate) to generate a map of the main effect of group at each voxel. This map was thresholded to generate a set of spatially contiguous 3D clusters of suprathreshold voxel statistics and the sum of each

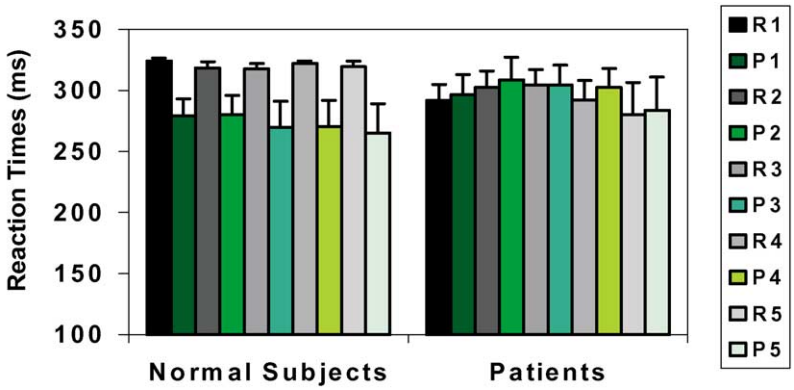

Fig. 2. Mean (+1 S.E.M.) reaction times (ms) over random (R1–R5; blocks 1 to 5 of random trials) and pattern trials (P1–P5; Blocks 1 to 5 of pattern trials) in healthy subjects and patients with schizophrenia.

3D cluster was tested against its non-parametrically ascertained null distribution (Bullmore et al., 1999b); cluster-wise one-tailed $p < 0.001$. The same inferential approach was used to identify voxels where there was a significant association between PL scores and power of activation in the group of normal subjects; although in this case the linear model was a simple regression of PL scores on power of response at each voxel. The general advantages of using computational inference to test null hypotheses about spatial statistics in brain imaging are rehearsed in Bullmore et al. (1999b). Briefly, spatial statistics are generally more sensitive and involve a smaller number of tests than voxel statistics, but their theoretical distributions under the null hypothesis may be over-conservative or intractable.

3. Results

3.1. Behavioral measures

Healthy subjects showed significant PL, but schizophrenic patients, as expected, did not (Group × Trial Type: Group: $F = 5.63$, $df = 1.10$, $p = 0.04$). There was no significant difference between patients and healthy controls for reaction times over the random trials, suggesting that patients did not show a generalized

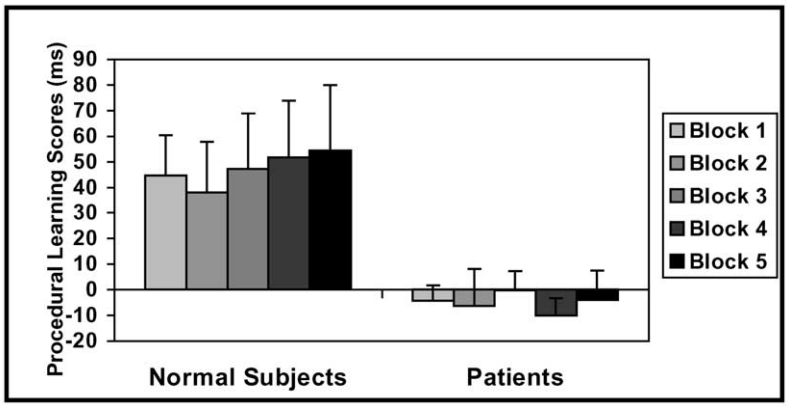

Fig. 3. Mean (+1 S.E.M.) procedural learning scores (ms) in healthy subjects and patients with schizophrenia.

performance deficit. Fig. 2 shows reaction times to pattern trials and random trials, and Fig. 3 shows the PL scores (mean reaction times to random trials *minus* mean reaction times to pattern trials) in normal and schizophrenic subjects. The data obtained during the first block (30-s OFF and 30-s ON) of trials demonstrated that normal subjects, but not patients, were able to gain from the practice session as they showed evidence of learning in the very first block of trials (Fig. 2). This, however, was not evident from the data (not shown) obtained during the practice session itself in healthy subjects.

3.2. Functional MRI

3.2.1. Generic brain activation mapping

The ON condition (pattern trials), in contrast to the OFF condition (random trials), elicited significant

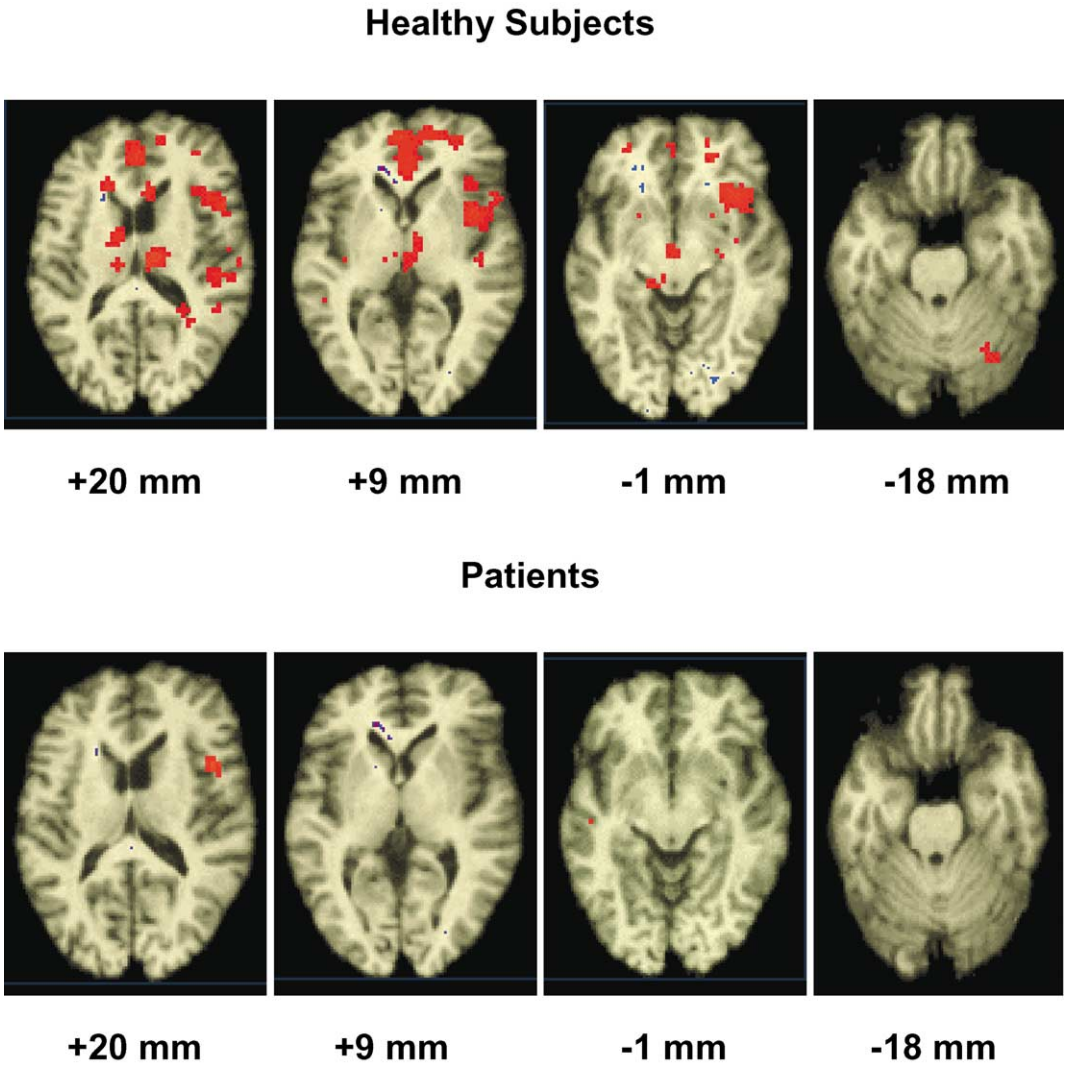

Fig. 4. Generic brain activation maps in healthy subjects (top row) and patients with schizophrenia (bottom row) during procedural learning. Major regions of activation in normal subjects are demonstrated in the striatum, thalamus, cingulate gyrus, insula and cerebellum (*z*-coordinates below each image). There is a lack of activation in patients. Images are left-right reversed.

Table 1
Main regions of activation in healthy subjects and patients with schizophrenia

Brodmann's area/region	Talaraich coordinates			Side	Number of voxels
	x	*y*	*z*		
Normal subjects					
32/Medial frontal lobe	−3	19	31	Left	49
32/Medial frontal lobe	9	50	9	Right	82
24/32/Medial frontal lobe	20	25	20	Right	19
24/Anterior-middle cingulate gyrus	0	33	4	Right	39
24/Anterior-middle cingulate gyrus	−3	19	26	Left	39
Insula	−35	11	9	Left	118
Insula	46	−8	15	Right	16
Striatum (caudate nucleus)	−6	−17	20	Left	17
Striatum (caudate nucleus)	14	−3	20	Right	11
Cerebellum	−29	−64	−18	Left	26
Thalamus	−3	−6	9	Left	16
Thalamus	6	−19	4	Right	10
45/Inferior frontal gyrus	−46	14	20	Left	45
10/Superior frontal gyrus	−14	56	4	Left	26
Patients					
45/Inferior frontal gyrus	−40	11	20	Left	45

activation in healthy subjects (search volume = 21,695; expected number of false positives = 20) mainly in Brodmann's area (BA) 24 and 32, striatum (caudate nucleus), thalamus, insula, and cerebellum, but not in patients (search volume = 17,749; expected number of false positives = 20) (Fig. 4). Table 1 presents the coordinates and magnitudes of all main activated regions in healthy subjects as well as in patients.

3.2.2. Differential activation in normal subjects and patients

We observed significant differences (total number of clusters in permutation distribution using 10 permutations = 1468, expected number of false positives = 1) between healthy subjects and patients in the thalamus, caudate nucleus and precuneus, with an additional focus now evident in the left sensor-

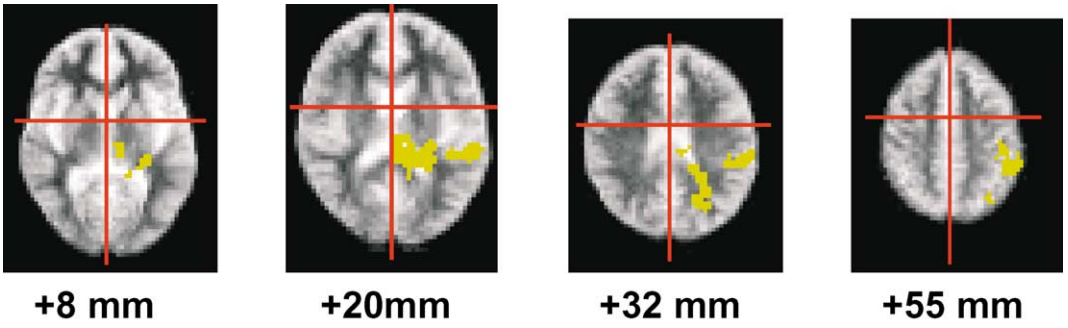

Fig. 5. Images demonstrating group difference between healthy subjects and patients in the thalamus (*x*, *y*, *z*: −10, −22,8; no. of voxels = 18), striatum (−16, −34,20; no. of voxels = 72), precuneus (−23, −51,32; no. of voxels = 60) and sensorimotor regions (−50, −33,55; no. of voxels = 92) (*z*-coordinates below each image), all left hemisphere.

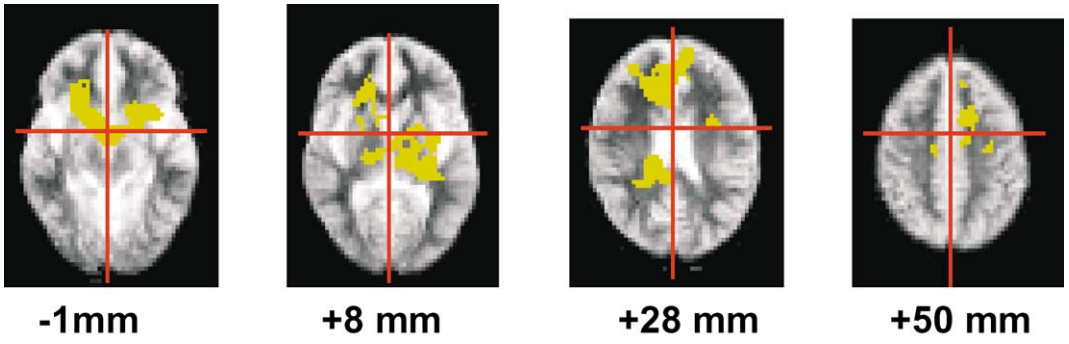

Fig. 6. Images demonstrating brain regions associated with the amount of procedural learning in healthy subjects. The regions are striatum (x,y,z: −2,11,−1; 16,26,8), thalamus (−18,−15,8), middle frontal lobe/anterior cingulate gyrus (−7,−36,28), posterior cingulate gyrus (−15,−33,28) and BA 6 (−14,−7,50) (z-coordinates below each image). Images are left-right reverse.

imotor region (see Fig. 5 for the coordinates and magnitudes of these regions).

3.2.3. Regression of procedural learning scores on power of activation in normal subjects

The regression of PL scores on power of activation (total number of clusters in permutation distribution using 10 permutations = 1214, expected number of false positives = 0) demonstrated that cerebral responses in the thalamus, striatum, precuneus, cingulate gyrus and BA 6 were related to PL magnitude in normal subjects (Fig. 6).

4. Discussion

Our findings are consistent with the previous literature in showing involvement of the striatum, cerebellum, thalamus, frontal and sensorimotor regions in PL in healthy subjects and, in addition, suggest that the precuneus may also be involved. In general, the association between the FPQ and PL scores and, to a lesser extent, changed activation pattern in the patient group and poor PL, strengthen the inference that, in healthy subjects, activation in the observed regions plays a causal role in PL.

Impaired PL in patients with Huntington's disease is thought to reflect a critical role of the striatum in this type of learning because of the major and presumably exclusive involvement of the caudate nucleus in this disease (Bruyn, 1968). This notion is well supported by our data. There have been suggestions of differential roles of the caudate nucleus and cerebellum in PL (Pascual-Leone et al., 1993), as patients with Parkinson's disease are able to improve their PL performance with a larger number of trials relative to the number required by healthy people; patients with cerebellar disorder fail to show such improvement. The influence of basal ganglia structures, in particular the caudate nucleus, on the prefrontal cortex is thought to be required for the timely access of information to and from a working memory buffer, whereas the cerebellum is thought to tap and order events in the time domain and be necessary for cognitive functions involving sequences (Salmon and Butters, 1995). Numerous observations in animals also indicate that the cerebellum is an important structure responsible for the procedural component of spatial event processing and learning (Petrosini et al., 1998).

The involvement of frontal regions in PL may be, as suggested earlier, via their connections to the basal ganglia. Alternatively, these regions may be directly involved in attention and error-checking mechanism reflected in rapid learning (Grafton et al., 1994). Left sensorimotor region (Fig. 5) and BA 6 (Fig. 6) were also found to be associated with PL which would be consistent with the increased right-handed motor requirement in healthy subjects, given that the task was dynamically paced, and would therefore respond more frequently, due to greater learning.

There is evidence for the involvement of the precuneus in the recall of visually guided saccades and in the organization of saccade sequences from memory (Berthoz, 1997), but not in spontaneous self-

paced or imagined saccades in darkness (Berthoz, 1997; Lang et al., 1995; Petit et al., 1993). The activation of the precuneus in normal subjects may, therefore, reflect specifically the difference between requirements for saccade generation in the control (saccades made randomly following the target) and experimental (organization of saccade sequence based on previous learning) conditions of the task. Other recent evidence supports direct precuneus association with PL, in particular, with consolidation (Tamminga, 2000) or the late phase (Hikosaka et al., 1999) of PL. Our current analysis of fMRI data (i.e. averaged activation over the entire 5-min experiment) does not shed light on activation patterns during early (the first blocks of random versus pattern trials) and relatively late (the last blocks of trials) phases of learning.

Another aspect of the experiment deserving comment is that all subjects had participated in a practice session prior to scanning. The behavioural data acquired during the very first block of random and pattern trials suggest that healthy subjects may have learnt the sequence during the practice session itself even though the behavioural data acquired during this session did not show this effect. It is thus possible that this study identified brain regions associated with recall, and not acquisition, of implicit knowledge about the sequences. Further research with more sophisticated analytic strategies and longer exposures (e.g. with inclusion of the practice session and repeated presentation of the task) is required to explore this possibility. Further research could also use different experimental designs to separate the reaction time (fine motor) and sequence learning (cognitive) components, the latter of which is more likely to involve higher cortical brain regions. This could not be achieved in this study because of the use of a standard box-car design to acquire fMRI data.

The patients with schizophrenia included in this study showed no evidence of PL and a lack of activation in relevant brain regions. They had a low level of symptoms and did not appear to suffer from low motivation as judged on the basis of the reaction times over random trials. Their performance deficits, thus, cannot be attributed to non-specific effects, for example, distracting effects of hallucinations or low motivation. There are indications that conventional antipsychotics, at least to some degree, may account for PL deficits in schizophrenic patients, perhaps via their strong dopamine D2 blocking actions in the striatum. Increased severity of tardive dyskinesia (a condition produced by medication with dopamine-blockers) in schizophrenics has been found to be associated with decreased motor procedural learning and shortened caudate nucleus T-2 relaxation times, using MRI (Granholm et al., 1993). Schizophrenic patients on conventional antipsychotics (Bedard et al., 1996) and normal volunteers treated with a conventional antipsychotic drug, haloperidol (Kumari et al., 1997), have also shown impaired PL. A number of recent studies (Bedard et al., 1996, 2000; Purdon et al., 2000; but see Kern et al., 1998) have reported an improvement on some measures of PL with atypical antipsychotics in patients with schizophrenia. It is thus possible that the lack of learning and the lack of activation in striatal regions in the patient group, as mentioned earlier, may be to some degree due to the administration of conventional antipsychotics.

The present experiment, however, showed differences between the patients and controls not only in the striatal region thought to be strongly associated with the administration of conventional antipsychotics, but also in thalamus, precuneus and sensorimotor regions. It is thus equally likely that differences between the patients and controls in striatal and thalamic regions reflect an aspect of the schizophrenic process involving disturbances in striatal, thalamic and frontal regions. Several studies have shown basal ganglia abnormalities in patients with schizophrenia, even in those with no prior exposure to antipsychotic treatment (e.g. Rubin et al., 1991; Brier et al., 1992; Buchsbaum et al., 1992). Furthermore, fronto-striatal dysfunction is proposed by many researchers as the underlying cause for symptoms of schizophrenia as well as other abnormalities such as deficits in eye movements and motor programming (e.g. Frith and Done, 1988; Robbins, 1990; Gray et al., 1991, Pantelis et al., 1992). The lack of activation in patients in the precuneus is perhaps explained by poor learning and thus no consolidation of learning phase in the patient group. Similarly, the lack of activation in the left sensorimotor region may be due to the lower number of responses made by patients as compared to controls during the pattern trial phase because of poor learning of sequences.

To conclude, the findings of this study demonstrated the involvement of the striatum, cerebellum, thalamus, cingulate gyrus, precuneus, and sensorimotor regions in PL. Schizophrenic patients had diminished PL scores and showed a lack of activation in relevant brain regions. The study, however, involved a small number of patients with low symptoms, was limited to male subjects only, and lacked adequate control groups (i.e. no group of drug-free schizophrenics or schizophrenics on atypical antipsychotics). Although the study helps to identify the brain regions involved in PL, it does not provide conclusive evidence whether impaired PL in schizophrenia is the result of conventional antipsychotics or reflects an aspect of the disease process. Further fMRI studies of PL in: (i) healthy subjects treated with conventional antipsychotics such as haloperidol (this, however, may be difficult to achieve for ethical reasons), (ii) drug-naïve schizophrenic patients, and (iii) schizophrenic patients receiving atypical antipsychotic drugs which produce less dopamine-blockade in the striatum would help to clarify these issues.

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References

Alexander, G.E., Crutcher, M.D., 1990. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci. 13, 266–271.

Barnes, T.R.E., 1989. A rating scale for drug-induced akathisia. Br. J. Psychiatry 154, 672–676.

Bedard, M., Scherer, H., Delorimier, J., Stip, E., Lanonde, P., 1996. Differential effects of D2- and D4 blocking neuroleptics on the procedural learning of schizophrenic patients. Can. J. Psychiatry 41, S21–S24.

Bedard, M., Scherer, H., Stip, E., Cohen, H., Rodbridge, J.P., Richer, F., 2000. Procedural learning in schizophrenia: further consideration on the deleterious effect of neuroleptics. Brain Cogn. 43 (1–3), 31–39.

Berthoz, A., 1997. Parietal and hippocampal contribution to topokinetic and topographic memory. Philos. Trans. R. Soc. London, Ser. B 352, 1437–1448.

Brammer, M., Bullmore, E.T., Simmons, A., Williams, S.C.R., Grasby, P.M., Howard, R.J.et al., 1997. Generic brain activation mapping in fMRI: a nonparametric approach. Magn. Reson. Imaging 15, 736–770.

Brier, A., Buchanan, R.W., Elkashef, A., Munson, R.C., Kirkpatrick, B., Gellad, F., 1992. Brain morphology and schizophrenia: a magnetic resonance imaging study of limbic, prefrontal cortex, and caudate structures. Arch. Gen. Psychiatry 49, 935–942.

Bruyn, G.W., 1968. Huntington's chorea: historical, clinical and laboratory synopsis. In: Vinken, P., Bruyn, G.W.Handbook of Clinical Neurology, vol. 6. North-Holland, Amsterdam, pp. 298–378.

Buchsbaum, M.S., Haier, R.J., Potkin, S.G., Nuechterlein, K., Bracha, H.S., Katz, M., Lohr, J., Wu, J., Lottenberg, S., Jerabek, P.A., 1992. Frontostriatal disorder of cerebral metabolism in never-medicated schizophrenics. Arch. Gen. Psychiatry 49 (12), 935–942.

Bullmore, E.T., Brammer, M., Williams, S.C.R., Rabe-Hesketh, S., Janot, M., David, A., Mellers, J., Howard, R., Sham, P., 1996. Statistical methods of estimation and inference for functional MR image analysis. Magn. Reson. Med. 35, 261–277.

Bullmore, E.T., Brammer, M.J., Rabe-Hesketh, S., Curtis, V.A., Morris, R.G., Williams, S.C.R. et al., 1999a. Methods for diagnosis and treatment of stimulus correlated motion in generic brain activation studies using fMRI. Hum. Brain Mapp. 7, 38–48.

Bullmore, E.T., Suckling, J., Overmeyer, S., Rabe-Hesketh, S., Taylor, E., Brammer, M.J., 1999b. Global, voxel, and cluster tests, for a difference between two groups of structural MR images of the brain. IEEE Trans. Med. Imaging 18 (1), 31–42.

Clare, L., McKenna, P.J., Mortiner, A.J., Baddeley, A.D., 1993. Memory in schizophrenia: what is impaired and what is preserved? Neuropsychologia 31, 1225–1241.

Cohen, N.J., Squire, L.R., 1980. Preserved learning and knowledge of analyzing skills in amnesia: dissociation of knowing how and knowing what. Science 201, 207–209.

Doyon, J., Own, A.M., Petrides, M., Sziklas, V., Evans, A.C., 1996. Functional anatomy of visuomotor skill learning in human subjects examined with positron emission tomography. Eur. J. Neurosci. 8, 637–648.

Doyon, J., Gaurdreau, D., Laforce, R., Castonguay, M., Bedard, M., Bedard, F., Bouchard, J.P., 1997. Role of the striatum, cerebellum, and frontal lobes in the learning of a visuomotor sequence. Brain Cogn. 34, 218–245.

Feldman, K.J., Kerr, B., Streissguth, A.P., 1995. Correlational analysis of procedural and declarative learning performances. Intelligence 20, 87–114.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1995. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P), Version 2. New York State Psychiatric Institute, Biometrics Research, New York.

Frith, C.D., Done, D.J., 1988. Towards a neuropsychology of schizophrenia. Br. J. Psychiatry 153, 437–443.

Goldberg, T.E., Saint-Cyr, J.A., Weinberger, D.R., 1990. Assessment of procedural learning and problem solving by tower of hanoi type tasks. J. Neuropsychiatry Clin. Neurosci., 165–173.

Goldberg, T.E., Torrey, E.F., Gold, J.M., Ragland, J.D., Bigelow, L.B., Weinberger, D.R., 1993. Learning and memory in monozygotic twins discordant for schizophrenia. Psychol. Med. 23, 71–85.

Gomez-Beldarrain, M., Garcia-Monco, J.C., Rubio, B., Pascual-Leone, A., 1998. Effect of focal cerebellar lesions on procedural learning in the serial reaction time task. Exp. Brain Res. 120, 25–30.

Gomez-Beldarrain, B., Grafman, J., Pascual-Leone, A., Garcia-Monco, J.C., 1999. Procedural learning is impaired in patients with prefrontal legions. Neurology 52, 853–1860.

Grafton, S.T., Woods, R.P., Tyszka, M., 1994. Functional imaging of procedural motor learning: relating cerebral flow with individual subject performance. Hum. Brain Mapp. 1, 221–234.

Grafton, S.T., Hazeltine, E., Ivry, R., 1995. Localization of independent cortical systems in human motor learning. J. Cognit. Neurosci. 7, 497–510.

Granholm, E., Bartzokis, G., Asarnow, R.F., Marder, S.R., 1993. Preliminary association between motor procedural learning, basal ganglia T2 relaxation times, and tardive dyskinesia in schizophrenia. Psychiatr. Res. Neuroimage 50, 33–44.

Gray, J.A., Feldon, J., Rawlins, J.N.P., Hemsley, D.R., Smith, A.D., 1991. The neuropsychology of schizophrenia. Behav. Brain Sci. 14, 1–84.

Green, M.F., Kern, K.S., Williams, O., McGurk, S., Kee, K., 1997. Procedural learning in schizophrenia: evidence from serial reaction time. Cognit. Neuropsychiatry 2 (2), 123–134.

Heindel, W.C., Salmon, D.P., Shults, C.W., Walicke, P.A., Butters, N., 1989. Neuropsychological evidence for multiple implicit memory systems: a comparison of Alzheimer's, Huntington's and Parkinson's disease patients. J. Neurosci. 9, 582–587.

Hikosaka, O., Nakahara, N., Rand, M.K., Sakai, K., Xiaofeng, L., Nakamura, K., Miyachi, S., Doya, K., 1999. Parallel neural networks for sequential procedures. Trends Neurosci. 22, 464–471.

Honda, M., Deiber, M., Ibanez, V., Pascual-Leone, A., Zhuang, P., Hallett, M., 1998. Dynamic cortical involvement in implicit and explicit motor sequence learning. A PET study. Brain 121, 2159–2173.

Jenkins, I.H., Brooks, J.G., Nixon, J.D., Frackowiak, R.S.J., Passingham, R.E., 1994. Motor sequence learning: a study with positron emission tomography. J. Neurosci. 14, 3775–3790.

Kay, S.R., Fishbein, A., Olper, L.A., 1987. The positive and negative syndrome scale. Schizophr. Bull. 13, 261–276.

Kern, R.S., Green, M.F., Marshall Jr., B.D., Wirshing, W.C., Wirshing, D., McGurk, S., Marder, S.R. 1998. Risperidone versus haloperidol on serial reaction time, manual dexterity, and motor procedural learning in treatment-resistant schizophrenic patients. Biol. Psychiatry 44 (8), 726–732.

Knopman, D., Nissen, M.J., 1991. Procedural learning is impaired in Huntington's disease: evidence from the serial reaction time task. Neuropsychologia 3, 245–254.

Knowlton, B.J., Mangels, J.A., Squire, L.R., 1996. A neostriatal habit learning system in humans. Science 273, 1399–1402.

Kumari, V., Corr, P.J., Cotter, P.A., Checkley, S.A., Gray, J.A., 1997. Effects of acute administration of d-amphetamine and haloperidol on procedural learning in man. Psychopharmacology 129, 271–276.

Lang, W., Petit, L., Holliger, P., Pietrzyck, U., Tzourio, N., Mazoyer, B., Berthoz, A., 1995. A positron emission tomography of oculomotor imagery. NeuroReport 5, 921–924.

Molinari, M., Leggio, M.G., Solida, A., Ciorra, R., Misciagna, S., Silveri, M.C., Petrosini, L., 1997. Cerebellum and procedural learning: evidence from focal cerebellar lesions. Brain 129, 1753–1762.

Ogawa, S., Lee, T.M., Kay, A.R., Tank, D.W., 1990. Brain magnetic resonance imaging with contrast dependent blood oxygenation. Proc. Natl. Acad. Sci. U. S. A. 87, 8868–8872.

Pantelis, C., Barnes, T.R.E., Nelson, E., 1992. Is the concept of frontal–subcortical dementia relevant to schizophrenia? Br. J. Psychiatry 160, 442–460.

Pascual-Leone, A., Grafman, J., Clark, K., Stewart, M., Massaquoi, S., Lou, J.S., Hallett, M., 1993. Procedural learning in Parkinson's disease and cerebellar degeneration. Ann. Neurol. 34, 594–602.

Petit, L., Orssaud, C., Tzourio, N., Salamon, G., Mazoyer, B., Berthoz, A., 1993. PET study of voluntary saccadic eye movements in humans: basal ganglia–thalamocortical system and cingulate cortex involvement. J. Neurophysiol. 69, 1009–1017.

Petrosini, L., Leggio, M.G., Molinari, M., 1998. The cerebellum in the spatial problem solving: a co-star or a guest star? Prog. Neurobiol. 56, 191–210.

Purdon, S.E., Mintz, A.R., Labelle, A., Waldie, B.D., 2000. Improvement of procedural learning in schizophrenia after six months of treatment with clozapine. Schizophr. Res. 41 (1), 184.

Robbins, T.W., 1990. The case for frontostriatal dysfunction in schizophrenia. Schizophr. Bull. 16, 391–402.

Rubin, P., Holm, S., Friberg, L., Videbech, P., Andersen, H.S., Bendsen, B.B., Stromso, N., Larsen, J.K., Lassen, N.A., Hemmingsen, R., 1991. Altered modulation of prefrontal and subcortical brain activity in newly diagnosed schizophrenia and schizopheniform disorder: a regional cerebral blood flow study. Arch. Gen. Psychiatry 48, 987–995.

Salmon, D.P., Butters, N., 1995. Neurobiology of skill and habit learning. Curr. Opin. Neurobiol. 5, 184–190.

Schmahmann, J.D., 1991. An emerging concept: the cerebellar contribution to higher function. Arch. Neurol. 48, 1178–1187.

Schwartz, B.L., Rosse, R.B., Veazey, C., Deutsh, S.I., 1996. Impaired motor skill learning in schizophrenia: implications for corticostriatal function. Biol. Psychiatry 39, 241–246.

Seger, C.A., 1994. Implicit learning. Psychiatr. Bull. 115, 163–196.

Simmons, A., Moore, E., Williams, S.C.R., 1999. Quality control for functional magnetic resonance imaging using automated data analysis and showchart charting. Magn. Reson. Med. 41 (6), 1274–1278.

Squire, L.R., Zola-Morgan, S., 1988. Memory: brain systems and behaviour. Trends Neurosci. 11, 170–175.

Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Human Brain. Thieme, Stuttgart.

Tamminga, C.A., 2000. Images in neuroscience. Am. J. Psychiatry 157 (2), 162.

Willingham, D.B., Koroshetz, W.J., Peterson, E.W., 1996. Motor skills and diverse neural bases: spared and impaired skill acquisition in Huntington's disease. Neuropsychology 10, 315–321.