Structural brain correlates of prepulse inhibition of the acoustic startle response in healthy humans

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Neural regions modulating prepulse inhibition (PPI) of the startle response, an operational measure of sensorimotor gating, are well established from animal studies using surgical and pharmacological procedures. The limbic and cortico-pallido-striato-thalamic circuitry is thought to be responsible for modulation of PPI in the rat. The involvement of this circuitry in human PPI is suggested by observations of deficient PPI in a number of neuropsychiatric disorders characterized by abnormalities at some level in this circuitry and recent functional neuroimaging studies in humans. The current study sought to investigate structural neural correlates of PPI in a sample of twenty-four right-handed, healthy subjects (10 men, 14 women). Subjects underwent magnetic resonance imaging (MRI) at 1.5 T and were assessed (off-line) on acoustic PPI using electromyographic recordings of the orbicularis oculi muscle beneath the right eye. Optimized volumetric voxel-based morphometry (VBM) implemented in SPM99 was used to investigate the relationship of PPI (prepulse onset-to-pulse onset interval 120 ms) to regional grey matter volumes, covarying for sex. Significant positive correlations were obtained between PPI and grey matter volume in the hippocampus extending to parahippocampal gyrus, basal ganglia including parts of putamen, globus pallidus, and nucleus accumbens, superior temporal gyrus, thalamus, and inferior frontal gyrus. These findings identify the relationship between PPI and grey matter availability on a highly spatially localized scale in brain regions shown to be activated in recent functional neuroimaging studies in association with PPI in healthy humans and demonstrate the validity of structural neuroimaging methods in delineating the neural mechanisms underlying human PPI.

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Introduction

Prepulse inhibition (PPI) of the startle response, a cross species phenomenon, refers to a reliable reduction in the amplitude of the response to a strong sensory stimulus (pulse) if briefly (by 30–500 ms) preceded by a weak stimulus (prepulse) (Graham, 1975). Presentation of the pulse at short lead intervals, while the prepulse is still being processed, presumably causes disrupted processing of, and thus an attenuated overt response to, this stimulus. The paradigms both in human and animal studies most commonly employ a loud noise as the pulse and a quieter noise as the prepulse. In human subjects, PPI is usually quantified as reduction in the eye blink response to a prepulse-plus-pulse trial compared to the response to a pulse-alone trial. Most human studies involving healthy as well as clinical populations have utilized passive task conditions (i.e., no specific instruction to attend the prepulse or the pulse) though some studies have required their subjects to specifically attend to the prepulse (review, Swerdlow et al., 1994). In animal studies, PPI is usually measured as reduction in the whole body startle (jump) response to a prepulse-plus-pulse trial compared to the response to a pulse-alone trial (review, Swerdlow et al., 1994). However, a recent study (Arnfred et al., 2004) of pigs using the eye blink startle response to assess PPI has confirmed PPI and its similar modulation (i.e., disruption) by a dopaminergic challenge to that seen with PPI of the whole body startle in rats (review; Swerdlow and Geyer, 1998).

Animal studies have shown that PPI is mediated by brain stem circuits involving the inferior colliculus, pedunculopontine tegmental nucleus, laterodorsal tegmental nucleus, substantia nigra pars reticulata, and caudal pontine reticular nucleus (Fendt et al., 2001), and modulated by forebrain circuits involving the prefrontal cortex, thalamus, hippocampus, amygdala, nucleus accumbens, striatum, ventral pallidum, globus pallidus, and subpallidal efferents to the pedunculopontine nucleus (reviews, Koch and Schnitzler, 1997; Swerdlow and Geyer, 1998; Swerdlow et al., 2001). Our recent study (Kumari et al., 2003a) using blood-oxygenation-level-
dependent functional magnetic resonance imaging (fMRI) of the entire brain during a tactile PPI paradigm demonstrated activation in the hippocampus, striatum, thalamus, and frontal and parietal cortical regions in healthy subjects and significantly less activation in all these regions in patients with schizophrenia (Kumari et al., 2003a). Indirect information on the neural substrates of human PPI is provided by observations of deficient PPI in a number of psychiatric and neurological disorders, including schizophrenia (review, Braff et al., 2001a), Huntington’s disease (Swerdlow et al., 1995), obsessive compulsive disorder (Swerdlow et al., 1993a), temporal lobe psychosis (Morton et al., 1994), and Tourette’s syndrome (Castellanos et al., 1996), which are known to be associated with abnormalities at some level in the circuitry considered to modulate PPI in animals (reviews, Koch and Schnitzler, 1997; Swerdlow and Geyer, 1998; Swerdlow et al., 2001).

The structural neural correlates of PPI in humans remain unexplored, although previous studies have utilized structural MRI volumetry to study the neural correlates of higher order cognitive functions (e.g., Ettinger et al., 2002, 2005; Maguire et al., 2000; Sanfilipo et al., 2002). This approach stems from the assumption that the volume of a brain region is an important tissue property (Armstrong, 1983; Ringo, 1991), reflecting its size and shape as well as the pattern of arrangement and densities of its cellular components (Caviness et al., 1996), and is closely associated with behavioral measures of its function. Recent data, for example, demonstrating a relationship between the behavioral measures of specific frontal lobe function and regional frontal lobe volumes (Ettinger et al., 2005; Sanfilipo et al., 2002) and between memory and spatial ability and hippocampal volumes (Maguire et al., 2000), have provided empirical support to this approach.

The present study aimed to investigate structural brain correlates of acoustic (passive) PPI in healthy human subjects using the voxel-based morphometry (VBM) technique which, rather than limiting the search to certain regions of interest (ROIs), allows the examination of correlations between grey matter availability and behavioral measures on a voxel-by-voxel basis across the entire brain (Gaser and Schlaug, 2003). On the basis of available (reviewed earlier) data, we predicted that PPI would be positively correlated with grey matter volume in the hippocampus/temporal lobe, striatum, thalamus, frontal, and possibly parietal regions.

Materials and methods

Subjects and design

Twenty-four right-handed subjects (10 men, 14 women; mean age [years] = 29.29, SD = 10.02) took part. Subjects were clinically screened for the exclusion criteria of DSM-IV Axis I and II disorders (First et al., 1996a,b) and neurological abnormalities. Subjects provided written, informed consent. The study procedures had approval from the ethics committee of the Institute of Psychiatry and Maudsley Hospital, London.

PPI and MRI data were acquired on the same day except for a few subjects who underwent PPI assessment the day before or after the scanning due to practical issues.

Psychophysiology data collection and analysis

A commercially available human startle response monitoring system (Mark II, SR-Lab, San Diego, CA) was utilized to generate and deliver the acoustic stimuli, and to record and score the electromyographic (EMG) activity for 250 ms starting from the onset of the acoustic startle stimulus. Acoustic stimuli were presented to subjects binaurally through headphones. The pulse-alone stimulus was a 40-ms presentation of 115-dB (A) white noise and the prepulse stimulus a 20-ms presentation of 85-dB (A) white noise, both over 70-dB (A) continuous background noise. The noise levels were calibrated using the continuous noise on a monthly basis. The session began with a 5-min acclimatization period consisting of 70-dB (A) continuous white noise. Subjects received four blocks of 18 trials each, after an initial pulse-alone trial; each block consisted of three pulse-alone trials, three prepulse trials with a 30-ms pulse-to-pulse (onset to onset) interval, three prepulse trials with a 60-ms pulse-to-pulse interval, three prepulse trials with a 90-ms pulse-to-pulse interval, three prepulse trials with a 120-ms pulse-to-pulse interval, and three prepulse trials with a 150-ms pulse-to-pulse interval presented to subjects in a pseudorandom order with a mean inter-trial interval of 15 s (range 9–23 s).

The experimental procedures for recording and scoring the startle reflexes were identical to those reported previously (e.g., Kumari et al., 2000, 2004). Eye blink component of the startle was indexed by recording EMG activity of the orbicularis oculi muscle directly beneath the right eye, by positioning two miniature silver/silver chloride electrodes. Recorded EMG activity was band-pass filtered, as recommended by the SR-Lab. A 50-hz filter was used to eliminate the 50-Hz interference. The EMG data were at first inspected on trial-to-trial basis offline (to exclude unusual trials for a particular subject) and scored by the analytic program of this system for response amplitude (in arbitrary analogue-to-digit units).

Subjects were told that the experiment was to measure their reactivity to a number of noise bursts, but no specific instructions were given as to attend or ignore them. They were requested to keep their eyes open during the experiment.

PPI was computed for each participant separately for each trial type as \((a - b/a)\) 100, where “\(a\)” = pulse-alone amplitude and “\(b\)” = amplitude over prepulse trials. Percent of PPI, rather than absolute amount of PPI (i.e., arithmetic difference between pulse-alone and prepulse trials), was used since this procedure eliminates the influence of individual differences in startle responsiveness. PPI at the 120-ms pulse-to-pulse interval was chosen as the main dependent measure for hypothesis testing because this interval produces the maximum PPI thus allowing the maximum power in terms of range of scores and is also the most frequently used interval in clinical studies (review, Braff et al., 2001a; Kumari et al., 2004). We chose to study 120-ms PPI rather the mean PPI across all prepulse-to-pulse intervals because (a) the neural correlates of PPI at different intervals may somewhat differ, and (b) focussing on a particular interval would facilitate a precise comparison of the results of future studies investigating structural brain correlates of human acoustic PPI with those of the present study.

MRI acquisition

Subjects underwent scanning on a 1.5 T GE Signa Advantage scanner (Milwaukee, WI). A high-resolution 3D inversion recovery prepared spoiled GRASS volume dataset was acquired in the AC–PC plane with TE = 5.3 ms, TI = 300 ms, TR = 12.2 s, in-plane resolution = 0.94 mm, and slice thickness = 1.5 mm.