Supplemental Materials and Methods

**Demographics.** We studied sixty two healthy subjects (33 males, mean age 31.8±8.1). Exclusion criteria included history of significant drug or alcohol abuse (no active drug use in the past year), head trauma with loss of consciousness, and any significant medical condition. Parental socio-economical status (Hollingshead Scale 42.9±17.2), handedness (Edinburgh Inventory 0.84±0.18), and total IQ (WAIS-R, 116.1±12.2) were measured. The present study was approved by the local IRB at the University of Bari. Moreover, after complete description of the study to the subjects, written informed consent was obtained. All data relative to these subjects have never been reported earlier.

**Genotype determination.** COMT Val^{158}Met genotype was determined as a restriction fragment length polymorphism after PCR amplification and digestion with *Nla*III (Bertolino et al., 2004b). Genotyping of the DAT1 40-bp repeat (VNTR) polymorphism in the 3’ untranslated region was determined using forward 5’-TGTGGTGTAGGGAACGGCCTGAG-3’ and reverse 5’-CTTCCTGGAGGTCACGGCTCAAGG-3’ primers. DNA amplification by polymerase chain reaction (PCR) of the 40-base pair repeat alleles was performed as described elsewhere (Szekeres et al., 2004). PCR products were separated by 4% agarose gel electrophoresis, visualized by ultraviolet transillumination and fragment sized by comparison with invitrogen 100bp DNA ladder. To confirm the results obtained with agarose gel electrophoresis, genomic DNA fragments were PCR-amplified using fluorescent labeled forward primer, resolved on an ABI Prism 3100 DNA sequencer (Applied Biosystems, Foster City, CA, USA) and analyzed with Genotyper software.

**Working Memory paradigm.** During fMRI, all subjects completed a blocked paradigm of the N-Back task (Bertolino et al., 2004b). Briefly, “N-back” refers to how far back in the sequence of stimuli the subject had to recall. The stimuli consisted of numbers (1-4) shown in random sequence and displayed at the points of a diamond-shaped box. There was a visually paced motor task which also served as a non-memory guided control condition (0-Back) that presented the same stimuli, but simply required subjects to identify the stimulus currently seen. In the working memory condition, the task required recollection of a stimulus seen two stimuli (2-Back) previously while continuing to encode additionally incoming stimuli. Performance data were recorded as the number of correct responses (accuracy) and as reaction time.
Acquisition and pre-processing of imaging data. Each subject was scanned using a GE Signa 3T scanner with a standard head-coil (Milwaukee, WI). Echo planar imaging BOLD fMRI data were acquired as described previously (TE=30 msec, TR= 2 seconds, 20 contiguous slices, voxel dimensions=3.75x3.75x5 mm) (Bertolino et al., 2004a; Bertolino et al., 2004b). We used a simple block design in which each block consisted of eight alternating 0-Back and 2-Back conditions (each lasting 30 seconds), obtained in 4 min and 8 sec, **120 whole-brain fMRI volumes**. The first four scans at the beginning of each time series were acquired to allow the signal to reach a steady state and were not included in the final analysis.

All fMRI data were reconstructed, registered, linear detrended, globally normalized, and then smoothed (10 mm Gaussian kernel) before analysis within SPM99. The registration parameters were extracted and used to exclude subjects with excessive inter-scan motion (>2 voxels translation, >1° rotation). **No subject was excluded from analysis based on these parameters**.

fMRI data were analyzed as a time series modeled by a sine wave shifted by an estimate of the hemodynamic response. Individual subject maps were created using \( t \) statistics (2-Back>0-Back). These individual contrast images were then used in second-level random effects models, that account for both scan-to-scan and subject-to-subject variability, to determine task-specific regional responses at the group-level with one-sample \( t \)-tests (main effects of task). As we were not interested in looking for differences in anatomical areas that were not activated in the main effect of task, we restricted the subsequent second level random effects analysis to only areas that were activated during the task. To facilitate this, a functional mask was created by using the **group** activation maps from 2-Back>0-Back contrasts (\( p<0.005 \), **minimum cluster size - \( k=3 \)**) limiting the analysis to the working memory cortical and subcortical network. Therefore, this procedure controls for the possibility that potential differences between the groups arise from areas that are engaged by only one of the groups. Because of our strong a priori hypothesis regarding the differential response of the working memory cortical network and our use of a rigorous random effects statistical model, we chose a statistical threshold of \( p<.005 \), \( k=3 \). Moreover, since areas within the working memory cortical network represented a priori regions of interest, we corrected for multiple comparisons the statistical threshold with a family wise error (FWE) small volume correction (using a 10mm radius sphere centered on prefrontal and cingulate coordinates published in previous studies, \( p<0.05 \) (Callicott et al., 1999; Callicott et al., 2000; Egan et al., 2001; Callicott et al., 2003b; Callicott et al., 2003a; Bertolino et al., 2004b)).
Statistical analysis for demographics and working memory performance. ANOVAs and $\chi^2$ were used to assess potential differences between all genotype groups (COMT, DAT, and COMT-DAT) for all demographic variables. Repeated measures ANOVA was used to evaluate the effect of genotypes on working memory accuracy and reaction time. Also, $\omega^2$ is an effect size measure which estimates the proportion of variance in a dependent measure accounted for by independent categorical variables in the population from which the sample was drawn. Thus, we used $\omega^2$ to measure the amount of variance in BOLD signal accounted for by both genotypes. $\omega^2$ is given by the equation: $\omega^2 = \frac{(SS_{\text{effect}} - (df_{\text{effect}})(MS_{\text{error}}))}{(MS_{\text{error}} + SS_{\text{total}})}$. 
REFERENCES


