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Neuroimaging and genetic associations of attentional and hypnotic processes

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Abstract

In the aftermath of the human genome project, genotyping is fast becoming an affordable and technologically viable complement to phenotyping. Whereas attempts to characterize hypnotic responsiveness have been largely phenomenological, data emanating from exploratory genetic data may offer supplementary insights into the genetic bases of hypnotizability. We outline our genetic and neuroimaging findings and discuss potential implications to top–down control systems. These results may explain individual differences in hypnotizability and propose new ideas for studying the influence of suggestion on neural systems.

Keywords: Attentional networks; Genetics; Suggestion; Hypnosis; Conflict reduction

1. Introduction

Cognitive neuroscience is the study of the neural mechanisms of behaviour. The past two decades have ushered in a new era of methodological advances in tools for non-invasive imaging of the living brain. Brain imaging has forged an impressive link between psychology and neuroscience. The information gleaned from such advances has been used to study both anatomical and functional aspects of neural processing (Posner, 2004). Functional neuroimaging methods allow one to measure changes in brain activity associated with simultaneous changes in behaviour, or in response to a wide variety of stimuli. Event-related potentials (ERP), functional magnetic resonance imaging (fMRI), magneto-encephalography (MEG), near infrared spectroscopy (NIRS), positron emission tomography (PET), and single photon emission computed tomography (SPECT) can all measure changes in brain activity.

Budding efforts to study hypnotic phenomena using neuroimaging have largely focused on cerebral blood flow, SPECT, PET, and a few fMRI studies (Baer et al., 1990; Crawford et al., 1998, 2000; Grond et al., 1995; Halligan et al., 2000; Kosslyn et al., 2000; Maquet et al., 1999; Rainville, 2002; Rainville et al., 1997, 1999, 2000, 2002; Szechtman et al., 1998; Walter et al., 1994). With the exception of ERPs, these neuroimaging assays have been sparsely employed in the examination of hypnotic phenomena but with intriguing results (Raz, 2004c; Raz et al., 2005). Genetic approaches investigating hypnotizability have been even more meager (Bauman and Bul, 1981; Ebstein et al., 1999; Lichtenberg et al., 2000; Morgan, 1973; Morgan et al., 1970; Rawlings, 1978).

In this paper we outline some of the recent findings relating attentional and hypnotic phenomena and focus on how gene association assays may illuminate hypnotizability.

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2. Attention

Because attention has a distinct anatomy that carries out basic psychological functions and that can be influenced by specific brain injuries and states, some researchers promoted the notion of attention as an organ system (Posner and Fan, in press). Attention selects aspects of the environment (e.g., objects) or ideas stored in our memory for conscious processing at any given time. Investigators have been studying attentional operations for about a century. William James argued that attending is the same as being aware, but unlike what he thought we now know that certain aspects of attention can be involuntary and can occur unconsciously. Since the 1980s human neuroimaging studies have allowed examination of the whole brain during tasks involving attention and consequently provided us with much information on how the brain houses these attentional processes (Posner and Fan, in press; Posner and Petersen, 1990). The ability to trace anatomical changes over time has provided methods for validating and improving pharmacological and other forms of therapy.

3. Attentional networks

Attention can be viewed as a system of anatomical areas carrying out the functions of alerting, orienting, and executive control (Raz and Buhle, 2006). In line with an attentional research agenda (Raz, 2004b,c; Raz and Buhle, 2006; Raz and Shapiro, 2002), we have recently devised a simple attention network test (ANT) that can be performed by adults, children, patients and even non-human animals (Fan et al., 2002). The ANT takes about half an hour to administer and provides three numbers that indicate the efficiency of the networks that perform the alert, orient and conflict resolution functions, respectively. Our previous work with this test has provided evidence on its reliability, its heritability, and the independence of the results for the three different attentional functions (Fan et al., 2001a,b; Fossella et al., 2002a,b).

Although previous studies have examined the areas involved in the components of the ANT (Corbetta et al., 2000; Hopfinger et al., 2000), recent research reported data concerning the brain areas involved in carrying out the ANT as a whole—first as a preliminary report (Fan et al., 2001a) and later more formally (Fan et al., 2005; Raz, 2004a). These fMRI findings suggest that this test activates three largely orthogonal networks related to components of attention (see Fig. 1). Pharmacological studies (e.g., Marrocco and Davidson, 1998) have related each of the networks with specific chemical neuromodulators: cholinergic systems arising in the basal forebrain play an important role in orienting; the norepinephrine (NE) system arising in the locus coeruleus of the midbrain is involved in alerting; and the anterior cingulate cortex (ACC) and lateral prefrontal cortex are target areas of the mesocortical dopamine system—involved in executive attention. fMRI activations (Fig. 1) of the cross-sectional view of the alerting network shows thalamic activation (i.e., alerting effect). The cross-sectional view of the orienting network shows parietal activation. And the cross-sectional view of the conflict network shows ACC activation.

4. Attentional and hypnotic phenomena

Hypnosis is often labeled as attentive receptive concentration (Spiegel and Spiegel, 1987). Indeed, evidence relating hypnotic phenomena to attentional mechanisms is mounting (Raz et al., 2002b) and there is general accord that hypnotic phenomena implicate attention (Karlin, 1979) and relate to self-regulation (Posner and Rothbart, 1998). Whereas a number of investigators have hypothesized that suggestibility correlates with underlying differences in individual patterns of waking attention (Tellegen and Atkinson, 1974), theories of hypnotic responding differ regarding attentional processes (Kirsch et al., 1999).

The marriage of attention and hypnosis led to a research agenda using hypnosis to examine disparate attentional networks (Raz and Shapiro, 2002). Drawing on behavioural (Raz et al., 2002b), optical (Raz et al., 2003), and neuroimaging assays (Raz et al., 2002a,b,d), we recently reported both the elimination and removal of Stroop interference under a specific posthypnotic suggestion to obviate reading in highly hypnotizable subjects (Raz et al., 2002b, 2003, 2005, 2006). These results are in line with published as well as unpublished case studies (MacLeod and Sheehan, 2003; Schatzman, 1980; Wheatley, 2003). However, replication of the wholesale group effect has been intangible for some researchers and further research needs to elucidate whether these differences are due to random variations or other methodological discrepancies.

In the classic Stroop task experienced readers are asked to name the ink color of a displayed word (Stroop, 1935). Responding to the ink color of an incompatible color word (e.g., the word "RED" displayed in blue ink), subjects are usually slower and less accurate than identifying the ink color of a control item (e.g., "***" or "LOT" inked in red). This difference in performance is called the Stroop interference effect (SIE) and is one of the most robust and well-studied phenomena in attentional research (MacLeod, 1992; MacLeod and MacDonald, 2000). Although there is gradual appreciation that word reading can be mediated by attention, it is still largely considered automatic because a proficient reader cannot withhold accessing the words' meaning despite explicit instructions to attend only to the ink color. Indeed, the standard account in both the word recognition and Stroop literatures maintains that words are automatically processed to the semantic level (MacLeod, 1991; Neely, 1991) and that the SIE is therefore the "gold standard" to study attentional measures (MacLeod, 1992). Nonetheless, our results (i.e., that effective posthypnotic suggestion consistently cancelled the SIE in highly hypnotizable individuals) indi-

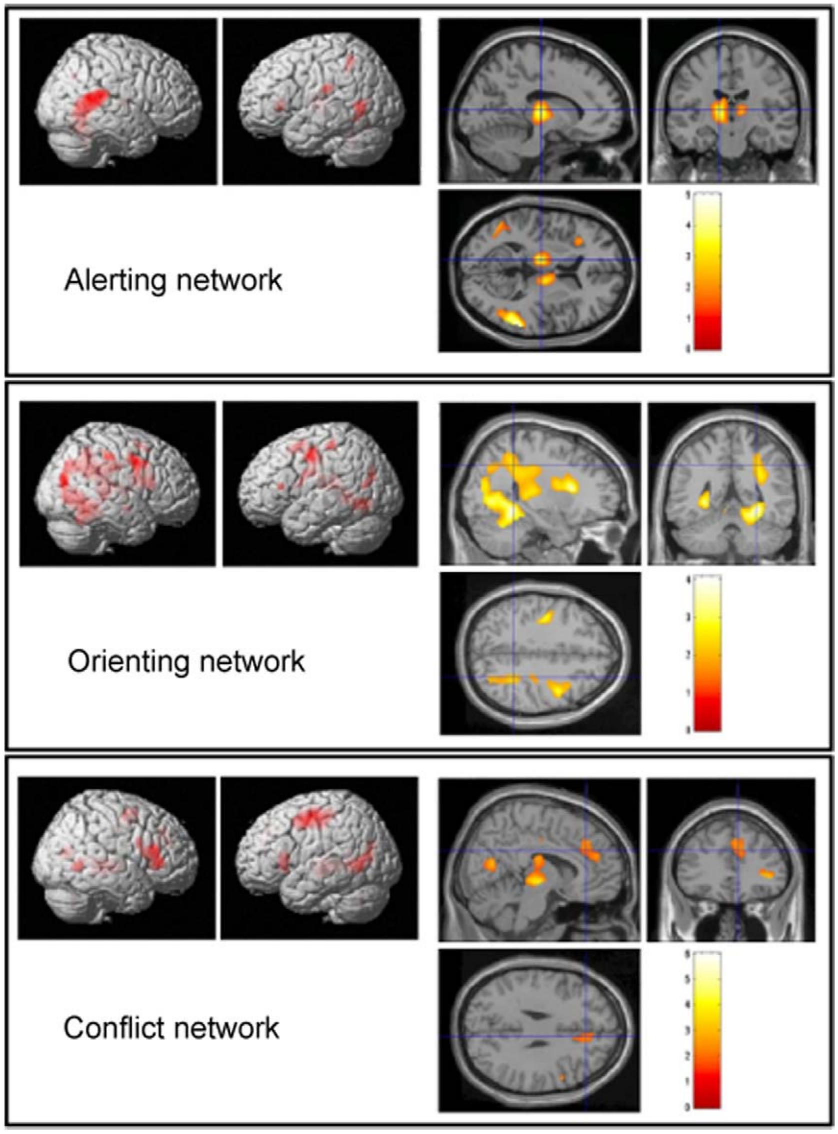

Fig. 1. Anatomy of attentional networks. fMRI images collected from sixteen healthy adults performing the ANT in a 3T GE magnet. Cross-sectional views of (1) the alerting network show thalamic activation (i.e., alerting effect), (2) the orienting network show parietal activation, and (3) the conflict network show ACC activation. First reported in a poster by Fan et al. (2001a), this figure outlines some of the functional anatomy subserving the distinct attentional networks. The pulvinar, superior colliculus, superior parietal lobe and frontal eye fields are often found active in studies of the orienting network; the anterior cingulate gyrus is an important part of the executive network (i.e., selective attention and conflict resolution), and the right frontal and parietal areas are active when people maintain the alert state (See also Fan and Posner, 2004; Fan et al., 2003b, 2005; Raz, 2004a; Raz and Buhle, 2006; Raz and Shapiro, 2002).

cate that the effect must operate via a top–down cognitive mechanism that modifies the processing of input words. Since the SIE typically activates the dorsal part of the ACC, these data support the view that monitoring conflict among potential responses involves the dorsal ACC (Botvinick et al., 2001).

Neuroimaging studies of executive attention have been conducted using either Stroop or Stroop-like tasks (Bush et al., 2000). Another frequently used conflict task requires a response to a central stimulus (e.g., an arrow pointing left) when it is surrounding by flankers that either point in the same direction (congruent) or in the opposite direction (incongruent). These conflict tasks have been shown by neuroimaging studies to activate midline frontal areas (e.g., ACC), and lateral prefrontal cortex. Thus, these experimental tasks provide a way to tease out the functional contributions of areas within the executive attention network. The preponderance of the evidence indicates that lateral prefrontal areas are involved in representing specific information over time (working memory), while medial ACC areas are related to the detection of conflict.

5. Using posthypnotic suggestion to reduce conflict in the human brain

Some researchers have attempted to explore the Stroop effect under hypnosis (Blum and Graef, 1971; Blum and Wiess, 1986; Dixon et al., 1990a; Dixon and Laurence, 1992; MacLeod and Sheehan, 2003; Nordby et al., 1999; Sheehan et al., 1988; Spiegel et al., 1985; Sun, 1994; Szechtman et al., 1998). However, these assays have largely concentrated on the effect of hypnosis without suggestion and often used non-classical Stroop paradigms (Sheehan et al., 1988). Historical single-case reports (MacLeod and Sheehan, 2003; Schatzman, 1980), esoteric publications (Sun, 1994), and informal personal communications (Wheatley, 2003) proposing hypnotic removal of Stroop conflict have not been rigorously pursued prior to our research efforts.

Multiple neuroimaging studies using variations of conventional Stroop tasks have activated a network of brain areas including the dorsal ACC. Requiring participants to respond to one dimension of a stimulus rather than a strong conflicting dimension (Botvinick et al., 2001; Bush et al., 2000; MacDonald et al., 2000), these data have resulted in a popular theory of cognitive control proposing that the ACC is part of a network involved in handling conflict between neural areas (Botvinick et al., 2001; Bush et al., 2000). While some researchers view the ACC through the lens of a conflict monitoring model (Botvinick et al., 2001; Cohen et al., 2000), others construe it as a regulation model engulfing broader processes of consciousness and self-regulation including executive attention and mentation (Bush et al., 2000).

To unravel the brain mechanism by which the post-hypnotic suggestion curtailed Stroop conflict (i.e., how suggestion affected visual processing), we studied highly hypnotizable (HH) and less hypnotizable (LH) participants both with and without a suggestion not to see the input as words. We complemented the superior spatial resolution of fMRI by event-related scalp electrical potentials (ERPs)—affording high temporal resolution—which were acquired separately while the same participants performed similar Stroop tasks. Data from this combined event-related fMRI and ERPs study recently illuminated the mechanism by which the posthypnotic suggestion to view Stroop words as foreign signs operated in HH subjects. The results show that the elimination of the Stroop conflict resulted in an attenuation of fMRI signal at the ACC and extrastriate areas (Raz et al., 2002a,b,d). Reports of these findings recently appeared in a number of accounts (Raz, 2004c; Raz and Buhle, 2006; Raz et al., 2005).

These data are consistent with reports that both attention and suggestion can modulate neural activity for visual stimuli (Kosslyn et al., 2000; Mack, 2002; Martinez et al., 1999; Rees et al., 1999). For example, by creating a situation in which subjects could look directly at a five-letter word without attending to it (i.e., they had to respond to a superimposed stream of pictures shown in different orientations), an fMRI study reported failure to perceive words even for decidedly familiar and meaningful stimuli placed at the center of gaze (Rees et al., 1999). Additionally, positron emission tomography (PET) data showed that HH individuals neither perceived color nor activated extrastriate areas related to color after they had been instructed to see a color pattern in gray-scale (Kosslyn et al., 2000). Finally, PET assays of pain showed that specific modulatory hypnotic suggestions could affect activation of different brain structures: whereas suggesting a drop in pain unpleasantness (i.e., pacifying conflict) reduced specific activity in ACC (Rainville et al., 1997), suggesting decreased pain intensity produced activity reduction in somatosensory cortex (Hofbauer et al., 2001). These accounts underline the influence attention and suggestion can impart to conflict situations and top–down cognitive control (Posner and Rothbart, 1998; Rainville, 2002; Rainville et al., 2002; Raz and Shapiro, 2002).

The higher temporal resolution afforded by scalp ERPs, whose source was localized more anteriorly, illustrated early reduction of brain waves under the experimental suggestion. Comparing the effects of suggestion (absent versus present) for the incongruent trials in the HH group, electrophysiological activity differed as early as 100 ms following word presentation (see Fig. 2). These data revealed that in contrast to no suggestion, the N1—an early ERP component thought to be related to directing attention to an information channel—was absent under suggestion, and posterior activity was not observed before 250 ms. These findings strongly propose that the absence of conflict was accomplished by changing the way visual input was processed. To relate the fMRI with the ERP data, brain electrical source analyses (BESA) explored the time course of the fMRI generators and provided evidence consistent with independent generators at both the ACC and cuneus.

In addition to data speaking to the reduced conflict resolution effect, using posthypnotic suggestion, the experimental design demonstrated how it is practically possible to dissociate attention based upon input processing from sensory activity based upon the input stream. While this outcome seems to leave as a puzzle how visual input got reduced by the posthypnotic suggestion—one possibility is that all input was reduced; another is that it was word specific—the ERP data tend to support the former. Furthermore, recent ERP data examining the error-related negativity (ERN), an electrophysiological index closely associated with commission of errors in cognitive tasks involving response conflict (Carter et al., 1998; Falkenstein et al., 1991; Gehring and Fencsik, 2001), showed that while the posthypnotic suggestion reduced conflict, it did not decrease conflict monitoring (Raz et al., 2005). Compared to the no posthypnotic suggestion condition, ACC activation decreased prior to response under suggestion, but then ACC activation increased upon incorrect responses on incongruent trials regardless of suggestion. Thus, it was possible to eliminate conflict resolution (i.e., early ACC diminution) yet maintain conflict monitoring (i.e., ACC activation following incorrect responses).

Finally, recent behavioural data collected from comparing hypnotic and non-hypnotic suggestions using a similar experimental protocol at the University of Connecticut also showed significant reduction, but not elimination, of Stroop conflict under both hypnotic and non-hypnotic suggestions (Pollard et al., 2003). Interpretation of these data

A

Anatomical structure	Brodmann's Area	X	Y	Z	Z-score	p	Voxels
Cuneus	17	-20	-67	14	3.49	.000	4416
Left middle frontal gyrus	6	-28	17	38	2.93	.002	257
Right cingulate gyrus	32	8	49	7	2.43	.008	258
Left insula		-34	-12	1	2.33	.010	188
Left inferior frontal gyrus	46	-36	28	10	2.23	.013	163
Right superior temporal gyrus	22	50	-10	4	2.23	.013	423

B C

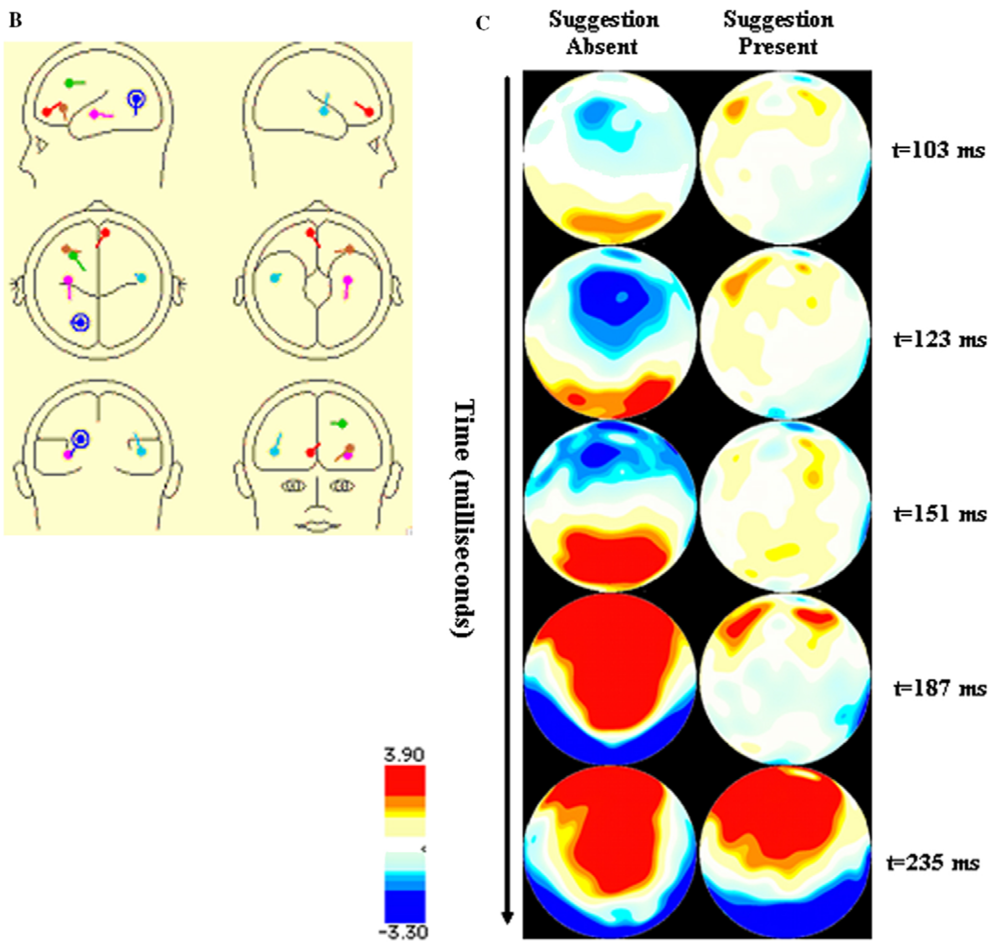

Fig. 2. Table A shows regions of significant fMRI activations on Stroop conflict comparing posthypnotic suggestion with no suggestion in highly suggestible individuals. The Talairach coordinates (x, y, z) for the maximally activated voxel in each of the regions and their Z-value are shown. To relate the fMRI with the ERP data, brain electrical source analyses (BESA) explored the time course of the fMRI generators. Figure B shows the six fixed dipoles placed at locations suggested by the fMRI data from Table 2A. The BESA algorithm provided evidence consistent with independent generators at both the anterior cingulate cortex and cuneus. Figure C shows representative ERP snapshots between 100 ms and 250 ms. These snapshots are taken from a video animation based on two-dimensional maps of scalp voltages, which were constructed by spherical spline interpolation mapping across twelve highly suggestible individuals on incongruent Stroop trials answered correctly as a function of suggestion. Within each pair, the right and left images indicate electrical activity with and without suggestion, respectively. Differences in activation patterns are seen 100–250 ms following word presentation. These data provide decisive evidence that, compared to the suggestion-absent condition, brain activity in posterior and anterior regions was largely removed following the experimental suggestion. These data support the notion that suggestion affected processing of the entire visual stream and was not specific to visual words.

proposed that susceptibility to suggestion, not explicit hypnotic procedures, may have been the critical factor underlying Stroop conflict reduction (Braffman and Kirsch, 1999; Kirsch and Braffman, 2001; Pollard et al., 2003).

6. Genetics of hypnotizability

Despite some general results, the genetic bases of hypnotizability remain largely unclear. The bulk of the evidence in the field dates 20–30 years ago and centers on twin data reported by Morgan et al. (Morgan, 1973; Morgan et al., 1970). Whereas the former study reports a correlation of 0.63 for monozygotic (MZ) twins and 0.08 for dizygotic (DZ) twins, the latter study reported 0.52 for MZ twins and 0.18 for DZ twins. Rawlings (1978) and Bauman and Bul (1981) echoed similar findings in subsequent reports. These data were not pursued further until the recent revolution in the field of genetics.

For more than a decade, the Human Genome Project has made great progress in the identification of the protean 30 000 genes in the human genome as well as the approximately 1.7 million polymorphic sites scattered across the six billion base-pair length of the human genome (Wolfsberg et al., 2002). These findings illuminate how genes influence disease development, aid scientists looking for genes associated with particular diseases, contribute to the discovery of new treatments, and afford insights into behavioural genetics (i.e., the relationship among certain genetic configurations and manifest behaviour).

Pioneering recent efforts to establish viable relations between phenotype and genotype, Richard Ebstein's group from Israel examined a number of such correlations, including an association between catechol–Omethionine-hyltransferase (COMT) high/low enzyme activity polymorphism and hypnotizability (Ebstein et al., 1999; Lichtenberg et al., 2000). Their data, using the Stanford hypnotic susceptibility scale form C (SHSS-C) administered in both Hebrew and English, revealed a significant difference in hypnotizability between subjects who carried the valine/methionine and valine/valine COMT genotypes.

Our fMRI data identified signal changes in neuroanatomical loci rich in dopaminergic innervation (e.g., ACC) (Raz et al., 2002d) and reduction of conflict as a result of posthypnotic suggestion (Raz, 2004c). Drugs known to affect the dopaminergic system as well as alter consciousness (e.g., propofol) seem to induce hypnosis-like experiences and modulate executive attention (DiFlorio, 1993; Fiset et al., 1999; Rainville et al., 2002; Xie et al., 2004). COMT is a gene that influences performance on prefrontal executive cognition and working memory tasks (Weinberger et al., 2001). Accordingly, we wanted to re-examine the results reported by Lichtenberg et al. (2000).

We compared variations in hypnotic susceptibility among healthy volunteers with differences in multiple dopaminergic genes from contributed DNA. We screened 80 subjects using the SHSS-C without the Anosmia to Ammonia item (Raz et al., 2002c). Each subject provided a small sample of DNA (via a sterile cheek swab), which was genotyped for a few well-known genetic polymorphisms in dopaminergic genes including DRD3, DRD4, MAOA, DAT, and COMT as previously described (Fossella et al., 2002).

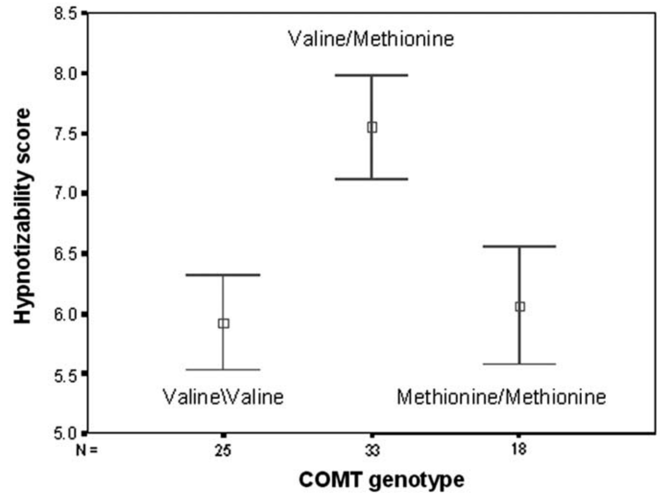

Fig. 3. COMT and hypnotizability. Distributions of COMT genotypes vs. SSHS-C hypnotizability score. The *Y*-axis shows hypnotizability scores (mean ± Standard error). The *X*-axis shows the distribution for each genotypic class at the COMT valine108/158 methionine polymorphism.

In line with data by Lichtenberg et al. (2000), we found a polymorphism in the COMT gene to be related to hypnotizability (see Fig. 3). Specifically, valine/methionine heterozygous subjects were more highly suggestible than either valine/valine or methionine/methionine homozygous subjects. The inverted U-shaped trend of valine/methionine COMT heterozygotes towards higher hypnotizability is congruent with data collected by other researchers (e.g., Lichtenberg et al., 2000) but differs from our previous studies examining the role of COMT in executive attention as measured by the ANT as well as by the Stroop (Sommer et al., 2004). Studies on the ANT found that subjects with the valine/valine genotype showed somewhat more efficient conflict resolution (lower SIE) than subjects with the valine/methionine genotype (Fossella et al., 2002). This trend was also seen in subjects who performed the Stroop task (Sommer et al., 2004). The valine allele of COMT, which confers relatively higher levels of enzyme activity and thus lower relative amounts of extrasynaptic dopamine, has been examined in the context of neuroimaging studies where it correlated with lower activity of the dorsolateral prefrontal cortex (Egan et al., 2001). Results from other genetic polymorphisms including DRD3, DRD4, MAOA and DAT showed no significant associations with hypnotizability.

7. Individual differences in attention and hypnotizability

Normal individuals differ in the efficiency of each of the attentional networks. For example, this can be examined by evaluating alerting, orienting and executive attention using the ANT. Self-report scales have also been used to study individual differences in attentional components. One higher-level factor called *effortful control* involves the ability to voluntarily shift and focus attention and inhibit certain information. Effortful control as reported by the subject seems to relate most closely to the executive attention network. Similar to the hypnosis data, here too twin studies have suggested that the difference between people in effortful control is highly heritable. Furthermore, individuals high in effortful control also report themselves as relatively low in negative emotion. This is one source of evidence supporting the idea that executive attention is important for control of both cognition and emotion.

Using modified Stroop procedures, some researchers have examined highly versus less hypnotizable subjects outside of hypnosis (Dixon et al., 1990b; Dixon and Laurence, 1992). Reliable differences were found between the groups. Stroop interference was significantly larger for the highly hypnotizables compared to the less hypnotizables (Raz et al., 2002b). This finding was taken to suggest that outside of the hypnotic context highly hypnotizables processed words more automatically than less hypnotizables. However, it also implies that the baseline efficiency of the executive attention network of highly hypnotizables deviates significantly from the baseline level of their less hypnotizable colleagues. In this regard, our nascent COMT findings may herald a genetic approach to hypnotizability whereby a genotype may suggest a "biological propensity" to complement an attentional phenotype (e.g., hypnotizability).

8. Conclusion

We outline close links between attentional and hypnotic mechanisms and provide some preliminary data to support a candidate gene approach to attention and hypnotizability. We have shown that neuroimaging assays and exploratory genetic associations from the domain of attentional research may illuminate hypnotic phenomena. Hypnosis is a complex phenomenon likely to be associated with many genetic polymorphisms. While COMT is not to be confused with the "hypnotizability gene", as data accumulate from multiple laboratories, meta-analyses of the various findings will likely increase our appreciation of genotyping as an important supplement to phenotyping (Fan et al., 2003a).

Since hypnosis can significantly alter performance for highly suggestible persons on attentional tasks such as the Stroop and ANT, our collective results support a potential common mechanism of dopaminergic modulation affecting both performance on attentional tasks and hypnotizability. Such a common mechanism may, however, overlap with different aspects of executive attention as suggested by an analysis of within-subject correlations of interference on the ANT and Stroop tasks (Sommer et al., in press). This approach may underline significant disparity between the cognitive capacities of highly and less-suggestible individuals and is likely to impact future research.

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