

Contextualizing specificity: Specific and non-specific effects of treatment

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Abstract

Modern medicine thrives on the ideal of specific diseases, and specificity has revolutionized thinking in clinical practice (e.g., psychiatry) as well as biomedical research (e.g., neuroscience). Different notions of specificity exist (e.g., clinical, biological, and behavioral). Behavioral specificity takes on new meaning in light of recent neuroimaging and genetic findings. Drawing on the metaphor of pharmacological specificity, we provide converging data suggesting that, at least for certain individuals, specific behavioral interventions can influence focal brain activations. Interpretation of these data paves the road to a more scientific strategy for studying the neural basis of suggestion and placebo response, and holds promise for the optimal matching of patient and treatment.

Keywords: Specificity, selectivity, psychotherapy, hypnosis, behavior, intervention, genetics, neuroimaging.

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The notion of specificity, of both disease etiology and therapeutic intervention, has been prominent within modern clinical and research disciplines, including in studies of the brain. The early contributions of Sydenham and the notion of “syndrome” probably constituted the first steps toward a modern model of disease (vs. the earlier notion of humoral “imbalance”). Thereafter, based upon identified etiologic agents and the therapeutic success of antitoxins or antibiotics, the “bacteriological” model of disease flourished. Specific disease concepts were also introduced into psychiatry in the 19th century, though at first with less influence than in physical medicine: many psychoanalysts argued that mental illnesses and health lay on a continuum of genetic and acquired factors, with illness differing only quantitatively from health.

Yet more recently, the concept of specificity has thrived with pharmacological applications in psychiatry. Pharmaceutical industry advertisements promote an unrefined, popular notion of specificity that outstrips existing data (Raz, 2006). For example, SSRIs are marketed for their ability to selectively block the reuptake of serotonin; yet they also influence several other receptor systems, instigating multiple effects. In fact, drugs often affect body systems that are seemingly unrelated to the presumed therapeutic effect (e.g., tricyclics and SSRIs have significant effects on fast sodium channels and platelet function, respectively). One meta-analysis of published randomized clinical trials reported that 75% of antidepressant response in adults was duplicated by placebo (Kirsch & Sapirstein, 1998). This initial meta-analysis was amply critiqued for multiple limitations (Klein, 1998). However, follow-up analyses to which these objections do not apply, again reported that about 80% of the response to antidepressants in adults was duplicated in placebo control groups (Kirsch & Moncrieff, 2007; Kirsch, Moore, Scoboria, & Nicholls, 2002; Moncrieff & Kirsch, 2005). Lastly, one drug can be effective for a variety of syndromes (e.g., SSRIs are effective for a wide assortment of symptoms ranging from obsessive-compulsive disorder and panic to major depression). Despite these accounts, the perception remains that pharmaceuticals are highly specific in both their biological action and therapeutic effect.

Psychological and Behavioral Specificity

Unlike pharmacological treatments, most psychotherapeutic interventions are now commonly perceived as nonspecific. This view, however, is fairly recent (Frank, 1963); psychodynamic interpretations were previously considered specific in both mechanism and therapeutic effect, and new evidence argues for a type of behavioral specificity that may be of research interest and clinical value.

With imaging of the living human brain, we can now show that psychotherapy influences neural processes through effects that are perhaps comparable to those achieved using pharmacological agents. In a positron emission tomography (PET) study of obsessive-compulsive disorder (OCD) patients, researchers compared the effects of behavioral therapy with those of fluoxetine (Baxter et al., 1992). Their data show that successful treatment, either pharmacological or behavioral, produces decreases in cerebral metabolic rates in specific brain structures. Replications and comparison with normal controls affirm that behavior therapy appears to “normalize” brain activation in OCD patients (Baxter et al., 1996; Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996). PET studies of individuals diagnosed with major depression and treated with either interpersonal psychotherapy or paroxetine show that symptom improvement correlates with changes in particular brain areas regardless of the form of intervention (Brody, Saxena, Mandelkern et al., 2001; Brody, Saxena, Stoessel et al., 2001). PET data from patients with social phobia treated with either citalopram or cognitive behavioral therapy (CBT) reveal that, in both forms of treatment, improvement is associated

with comparable changes in cerebral blood flow (Furmark et al., 2002). Moreover, the degree of change in blood flow was associated with clinical improvement one year later. More recent data from fMRI show that psychotherapeutic interventions (e.g., CBT) are associated with modifications of the dysfunctional neural circuitry associated with anxiety disorders (e.g., arachnophobia) (Paquette et al., 2003) and schizophrenia (Wykes et al., 2002). These findings demonstrate that cognitive and behavioral modifications in a psychotherapeutic context are associated with regional metabolic changes in the brains of patients with major depression or anxiety-related disorders.

Behavioral Specificity and Focal Brain Areas

Freud argued that the effects of psychoanalysis were not based on suggestion, yet for some, hypnosis provides the fundamental model for understanding psychotherapy. For example, the therapeutic element of psychoanalysis may be suggestibility via transference—with the difference between the two being one of terminology (Chertok & Stengers, 1992). For “highly suggestible individuals,” hypnotic suggestion can instigate physiological changes, which are seldom experienced in common wakefulness (Raz & Shapiro, 2002). These changes are occasionally akin to those observed with biological interventions (Baxter et al., 1992; Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996). Although little studied in mainstream medicine, these changes are likely a vital clue to the behavioral and therapeutic efficacy of suggestion (Raz, 2004a, 2004b; Raz & Buhle, 2006; Raz, Keler, Norman, & Senechal, 2007; Raz, Kirsch, Pollard, & Nitkin-Kaner, 2006; Raz, Moreno-Iniguez, Martin, & Zhu, 2007).

For instance, drawing on behavioral (Raz, Shapiro, Fan, & Posner, 2002), optical (Raz et al., 2003), and neuroimaging studies (Raz, Fan, & Posner, 2005), we recently reported the elimination of the Stroop Interference Effect (SIE) in highly suggestible subjects under a specific posthypnotic suggestion to construe English text as meaningless symbols in an unfamiliar language, showing that even some of the components of a vigorous effect, such as reading, might be dampened down by a top-down cognitive mechanism summoned by suggestion.

Furthermore, requiring people to respond to one dimension of a stimulus, rather than a strong conflicting dimension, activates both midline frontal areas and lateral prefrontal cortex. Since the SIE typically activates the dorsal part of the anterior cingulate cortex (ACC), these data seem to support the view that suggestion can influence a focal brain function, prompting a specific behavioral effect (Raz, 2004b; Raz, Fan, & Posner, 2005). While no current drug can achieve such specific modulation of neural activity in the ACC, this intervention depends on the characterization of individuals who are susceptible to suggestion.

The Genetics of Suggestibility and Individual Differences in Attention

Although the genetic bases of human suggestibility remain largely unclear, recent studies found an association between catechol-O-methioninehytransferase (COMT) activity polymorphism and suggestibility (Lichtenberg, Bachner-Melman, Ebstein, & Crawford, 2004; Lichtenberg, Bachner-Melman, Gritsenko, & Ebstein, 2000; Raz, 2005; Raz, Fan, & Posner, 2006). COMT is a gene that influences performance on prefrontal executive cognition and working memory tasks. It has “valine” and “methionine” alleles; valine/methionine heterozygous subjects appear more highly suggestible than either valine/valine or methionine/methionine homozygous subjects. The finding that heterozygotes’ trend toward higher suggestibility complements the exploratory efforts examining the role of COMT in executive attention. These studies report enhanced focal attention for carriers of this genotype (Raz, Fan, & Posner, 2006) and are consonant with recent dopaminergic models (Bilder, Volavka, Lachman, & Grace, 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 correlates with reduced activity in the dorsolateral prefrontal cortex (Egan et al., 2001). Genetic assays of attention report that subjects with the valine/valine genotype show somewhat more efficient conflict resolution (i.e., less interference) than subjects with the other genotypes (Raz, 2005; Raz, Fan, & Posner, 2006). These collective data are helpful in the nascent quest to identify highly suggestible individuals and classify individual attentional profiles (Raz, 2004a; Raz & Buhle, 2006).

Conclusion

We submit that, at least for certain individuals, behavioral specificity can be as compelling as pharmacological specificity. Behavioral interventions, suitably designed for susceptible individuals, can influence cognition, emotion, thought and action via focal neural activations. Moreover, given that suggestion can influence the activity of brain foci, more effort should be directed toward understanding the effects of expectation, context, suggestion and placebo (Price, Craggs, Verne, Perlstein, & Robinson, 2007; Sharav & Tal, 2006, , 2007; Wager et al., 2004).

In the aftermath of the human genome and neuroimaging revolutions, a future time before long may permit identification of suggestible patients and selection of psychological treatment (e.g., based on genetic screening, attentional testing, and personality profiles such as suggestibility). In such a world, neuroimaging will help in deciding which patient should be treated by drugs and which by psychotherapy, as well as providing an objective guide to the effects of treatment.

References

- Baxter, L. R., Jr., Saxena, S., Brody, A. L., Ackermann, R. F., Colgan, M., Schwartz, J. M., Allen-Martinez, Z., Fuster, J. M., & Phelps, M. F. (1996). Brain mediation of obsessive-compulsive disorder symptoms: Evidence from functional brain imaging studies in the human and nonhuman primate. *Seminars in Clinical Neuropsychiatry*, 1(1), 32-47.
- Baxter, L. R., Jr., Schwartz, J. M., Bergman, K. S., Szuba, M. P., Guze, B. H., Mazziotta, J. C., Alazraki, A., Selin, C. E., Ferng, H. K., Munford, P., et al. (1992). Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. *Archives of General Psychiatry*, 49(9), 681-689.
- Bilder, R. M., Volavka, J., Lachman, H. M., & Grace, A. A. (2004). The catechol-O-methyltransferase polymorphism: Relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology*, 29(11), 1943-1961.
- Brody, A. L., Saxena, S., Mandelkern, M. A., Fairbanks, L. A., Ho, M. L., & Baxter, L. R. (2001). Brain metabolic changes associated with symptom factor improvement in major depressive disorder. *Biological Psychiatry*, 50(3), 171-178.
- Brody, A. L., Saxena, S., Stoessel, P., Gillies, L. A., Fairbanks, L. A., Alborzian, S., Phelps, M. E., Huang, S. C., Wu, H. M., Ho, M. L., Ho, M. K., Au, S. C., Maidement, K., & Baxter, L. R., Jr. (2001). Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy: Preliminary findings. *Archives of General Psychiatry*, 58(7), 631-640.

- Chertok, L., & Stengers, L. (1992). *A Critique of psychoanalytic reason: Hypnosis as a scientific Problem from Lavoisier to Lacan* (p. 319). Stanford, CA: Stanford University Press.
- Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicott, J. H., Mazzanti, C. M., Straub, R. E., Goldman, D., & Weinberger, D. R. (2001). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences (USA)*, 98(12), 6917-6922.
- Frank, J. D. (1963). *Persuasion and healing: A comparative study of psychotherapy*. New York: Schocken Books.
- Furmark, T., Tillfors, M., Marteinsdottir, I., Fischer, H., Pissiota, A., Langstrom, B., & Fredrikson, M. (2002). Common changes in cerebral blood flow in patients with social phobia treated with citalopram or cognitive-behavioral therapy. *Archives of General Psychiatry*, 59(5), 425-433.
- Kirsch, I., & Moncrieff, J. (2007). Clinical trials and the response rate illusion. *Contemporary Clinical Trials*, 28(4), 348-351.
- Kirsch, I., Moore, T. J., Scoboria, A., & Nicholls, S. S. (2002). The emperor's new drugs: An analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. *Prevention and Treatment*, 5(23).
- Kirsch, I., & Sapirstein, G. (1998). Listening to Prozac but hearing placebo: A meta-analysis of antidepressant medication. *Prevention and Treatment*, 1.
- Klein, D. F. (1998). Listening to meta-analysis but hearing bias. *Prevention and Treatment*, 1.
- Lichtenberg, P., Bachner-Melman, R., Ebstein, R. P., & Crawford, H. J. (2004). Hypnotic susceptibility: Multidimensional relationships with Cloninger's Tridimensional Personality Questionnaire, COMT polymorphisms, absorption, and attentional characteristics. *International Journal of Clinical and Experimental Hypnosis*, 52(1), 47-72.
- Lichtenberg, P., Bachner-Melman, R., Gritsenko, I., & Ebstein, R. P. (2000). Exploratory association study between catechol-O-methyltransferase (COMT) high/low enzyme activity polymorphism and hypnotizability. *American Journal of Medical Genetics*, 96(6), 771-774.
- Moncrieff, J., & Kirsch, I. (2005). Efficacy of antidepressants in adults. *British Medical Journal*, 331(7509), 155-157.
- Paquette, V., Levesque, J., Mensour, B., Leroux, J. M., Beaudoin, G., Bourgouin, P., & Beaugard, M. (2003). Change the mind and you change the brain: Effects of cognitive-behavioral therapy on the neural correlates of spider phobia. *Neuroimage*, 18(2), 401-409.
- Price, D. D., Craggs, J., Verne, G. N., Perlstein, W. M., & Robinson, M. E. (2007). Placebo analgesia is accompanied by large reductions in pain-related brain activity in irritable bowel syndrome patients. *Pain*, 127(1-2), 63-72.
- Raz, A. (2004a). Anatomy of attentional networks. *The Anatomical Record Part B: The New Anatomist*, 281(1), 21-36.
- Raz, A. (2004b). Atypical attention: Hypnosis and conflict reduction. In M. I. Posner (Ed.), *Cognitive neuroscience of attention* (pp. 420-429). New York: Guilford Publications.
- Raz, A. (2005). Attention and hypnosis: Neural substrates and genetic associations of two converging processes. *International Journal of Clinical and Experimental Hypnosis*, 53(3), 237-258.

- Raz, A. (2006). Perspectives on the efficacy of antidepressants for child and adolescent depression. *PLoS Med*, 3(1), e9.
- Raz, A., & Buhle, J. (2006). Typologies of attentional networks. *Nature Reviews Neuroscience*, 7(5), 367-379.
- Raz, A., Fan, J., & Posner, M. I. (2005). Hypnotic suggestion reduces conflict in the human brain. *Proceedings of the National Academy of Sciences (USA)*, 102(28), 9978-9983.
- Raz, A., Fan, J., & Posner, M. I. (2006). Neuroimaging and genetic associations of attentional and hypnotic processes. *Journal of Physiology*, 99(4-6), 483-491.
- Raz, A., Keller, S., Norman, K., & Senechal, D. (2007). Elucidating Tourette's Syndrome: Perspectives from hypnosis, attention and self-regulation. *American Journal of Clinical Hypnosis*, 49(4), 289-309.
- Raz, A., Kirsch, I., Pollard, J., & Nitkin-Kaner, Y. (2006). Suggestion reduces the Stroop effect. *Psychological Science*, 17(2), 91-95.
- Raz, A., Landzberg, K. S., Schweizer, H. R., Zephrani, Z. R., Shapiro, T., Fan, J., & Posner, M. I. (2003). Posthypnotic suggestion and the modulation of Stroop interference under cycloplegia. *Conscious and Cognition*, 12(3), 332-346.
- Raz, A., Moreno-Iniguez, M., Martin, L., & Zhu, H. (2007). Suggestion overrides the Stroop effect in highly hypnotizable individuals. *Conscious and Cognition*, 16(2), 331-338.
- Raz, A., & Shapiro, T. (2002). Hypnosis and neuroscience: A cross talk between clinical and cognitive research. *Archives of General Psychiatry*, 59(1), 85-90.
- Raz, A., Shapiro, T., Fan, J., & Posner, M. I. (2002). Hypnotic suggestion and the modulation of Stroop interference. *Archives of General Psychiatry*, 59(12), 1155-1161.
- Schwartz, J. M., Stoessel, P. W., Baxter, L. R., Jr., Martin, K. M., & Phelps, M. E. (1996). Systematic changes in cerebral glucose metabolic rate after successful behavior modification treatment of obsessive-compulsive disorder. *Archives of General Psychiatry*, 53(2), 109-113.
- Sharav, Y., & Tal, M. (2006). Focused hypnotic analgesia: Local and remote effects. *Pain*, 124(3), 280-286.
- Sharav, Y., & Tal, M. (2007). Response to editorial on Sharav and Tal (2006). *Pain*, 127(1-2), 195; author reply 195-196.
- Wager, T. D., Rilling, J. K., Smith, E. E., Sokolik, A., Casey, K. L., Davidson, R. J., Kosslyn, S. M., Rose, R. M., & Cohen, J. D. (2004). Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science*, 303(5661), 1162-1167.
- Wykes, T., Brammer, M., Mellers, J., Bray, P., Reeder, C., Williams, C., & Corner, J. (2002). Effects on the brain of a psychological treatment: cognitive remediation therapy: functional magnetic resonance imaging in schizophrenia. *British Journal of Psychiatry*, 181, 144-152.