

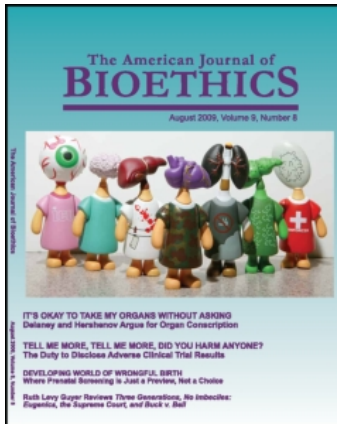
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Unintended Changes in Cognition, Mood, and Behavior Arising from Cell-Based Interventions for Neurological Conditions: Ethical Challenges

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Target Article

Unintended Changes in Cognition, Mood, and Behavior Arising from Cell-Based Interventions for Neurological Conditions: Ethical Challenges

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The prospect of using cell-based interventions (CBIs) to treat neurological conditions raises several important ethical and policy questions. In this target article, we focus on issues related to the unique constellation of traits that characterize CBIs targeted at the central nervous system. In particular, there is at least a theoretical prospect that these cells will alter the recipients' cognition, mood, and behavior—brain functions that are central to our concept of the self. The potential for such changes, although perhaps remote, is cause for concern and careful ethical analysis. Both to enable better informed consent in the future and as an end in itself, we argue that early human trials of CBIs for neurological conditions must monitor subjects for changes in cognition, mood, and behavior; further, we recommend concrete steps for that monitoring. Such steps will help better characterize the potential risks and benefits of CBIs as they are tested and potentially used for treatment.

Keywords: CNS, personal identity, risks, stem cells

The prospect of using cell-based interventions (CBIs) to treat neurological conditions raises several important ethical and policy questions, such as the permissibility of using embryo- or fetal-derived cells, the permissibility of creating human/nonhuman chimeras for research (Streiffer 2005; Robert 2006), what constitutes reasonable evidence

of safety and efficacy for purposes of allowing translation from animal models to human subjects research (Regenber et al. 2008), and whether the rush to translation in stem cell research might itself impede advances in the basic biological research (Maienschein et al. 2008). In this target article, we focus on less well-charted issues related to the unique

Acknowledgment: The authors acknowledge the contribution of Dr. Ira Black, who died before the completion of the manuscript. Address correspondence to D. J. H. Mathews, PhD, Johns Hopkins University, 624 North Broadway, Hampton House 352, Baltimore, MD 21205. E-mail: dmathews@jhmi.edu

constellation of traits that characterize CBIs targeted at the central nervous system (CNS). In particular, there is at least a theoretical prospect that these cells will alter the recipients' cognition, mood, and behavior—brain functions that are central to our concept of the self (especially to our personality, character, and agency). Some changes, such as recovery of functions lost due to brain injury or disease, will be desirable and intended effects of the intervention. However, the potential for changes in recipients' cognition, mood, or behavior, though perhaps remote, is cause for concern and careful ethical analysis: work that is made more difficult by the absence of data on which to judge the likelihood and magnitude of such changes.

Both to enable better informed consent in the future and as an end in itself, we argue that early human trials of CBIs for neurological conditions must monitor subjects for changes in cognition, mood, and behavior; further, we recommend concrete steps for that monitoring. Such steps will help better characterize the potential risks and benefits of CBIs as they are tested and potentially used for treatment.

CONTEXT

Concerns about changes affecting the self are motivated by factors relating both to the mechanism of action of CBIs and the site of intervention of such interventions for neurological conditions. First, the potential therapies under consideration involve novel CBIs: such therapies are poorly understood, when compared with pharmacological and surgical interventions that are more commonly employed. Second, the therapies are targeted at the CNS, and in many cases, specifically at the brain, where neural circuitries underlie the psychological characteristics that are central to the self.

It is important to keep in mind from the outset that the conditions for which CBIs are currently being considered are serious, sometimes fatal, neurological conditions in which the brain is already functioning abnormally in some way (a notable exception being spinal cord injury). As such, we presume that most persons would view the risk of cognitive, affective, or behavioral changes as relatively insignificant compared with the potential benefits. Nonetheless, it is critical that during the informed consent process, the risks be characterized such that potential research participants have sufficient information to provide valid informed consent (Master et al. 2007; Mathews et al. 2008).

POTENTIAL CHANGES ARISING FROM CELL-BASED INTERVENTIONS

While current models of brain function may do a reasonable job of explaining aspects of many everyday cognitive functions as well as how pathological processes (e.g., dementias and other neurodegenerative disorders) can alter or diminish those functions, it is considerably more challenging at this stage to extend these models to explain how the brain can be repaired or reorganized (e.g., in recovery from stroke) (Hillis 2005; Zhang et al. 2005) and how it might be “rebuilt”

using CBIs (e.g., in neurodegenerative disorders) (Lindvall et al. 2004; Oliveira and Hodges 2005). Given the gaps in our knowledge about the brain, any predictions we make about the risks of CBIs are highly speculative and perhaps prone to exaggeration. It is important to stress that the types of changes discussed here are hypothetical at this stage. Although it is difficult (some would argue impossible) to extrapolate the probability of higher-order functional changes from studies that employ animal models of the relevant neurological conditions (Regenberg et al. 2008), it is nevertheless important to monitor for such effects in preclinical studies (Greene et al. 2005).

We likely will not have a clear picture of the risk profile for these types of interventions until clinical trials in humans are well underway. However, there are analogous cases from non-CBIs in humans in which such changes have occurred, demonstrating not only that such side effects are not novel, but also that they are tolerated in certain circumstances. Medical management of Parkinson's disease (PD) has been associated with serious side effects, ranging from levodopa-induced dyskinesias (involuntary movements) to striking behavioral changes such as development of pathological gambling problems (Dodd et al. 2005). Deep brain stimulation for PD and other movement disorders has been shown to induce changes in mood such as depression or mania (Bejjani et al. 1999; Berney et al. 2002; Kulisevsky et al. 2002) and changes in behavior, such as hypersexuality (Temel et al. 2006). Electroconvulsive therapy, which can be effective for otherwise treatment-refractory depression, is known to cause transient cognitive problems (Datto 2000; O'Connor et al. 2003; Schulze-Rauschenbach et al. 2005). Even treatment for non-neurological conditions may induce neurological changes. For example, a number of common drugs (e.g., naproxen, diphenhydramine) can cause cognitive changes in the elderly (Goodwin and Regan 1982; Agostini et al. 2001), although such changes are reversible by stopping drug administration (this effect is not anticipated to be the case for CBIs, for which the intervention consists of living cells), and cancer treatment can cause cognitive changes in women with breast cancer (Burstein 2007), though the reasons for such side effects are not necessarily clear. While these are merely analogies—and there may be no reason to believe that CBIs would carry these particular risks—they suggest that we should anticipate the possibility of altering cognition, mood, or behavior when testing new neurological interventions (Glannon 2007).

What Types of Changes Might Occur?

Some changes in cognition, mood, and behavior resulting from CBIs for neurological conditions would, of course, be intended as part of the therapeutic goal. For example, successful treatment of a pediatric metabolic disorder such as Batten disease would entail improvement in cognition and behavior relative to the natural history of the disorder. Similarly, a successful CBI for Alzheimer's disease would involve improvement of cognition and would prevent or

delay progression to severe cognitive impairment characteristic of later stages of the disease.

Beyond such therapeutic effects, there may be changes that are not sought through the intervention and are not commonly thought of as adverse events, but which nonetheless raise concerns. A CBI involving implantation of allogeneic (non-self) cells is a type of transplant, in which the recipient receives donor brain material. This could raise concern among some that the recipient might acquire traits of the donor, perhaps even undergoing changes so marked that the recipient becomes almost unrecognizable in affect or cognitive capacity relative to her prior state. (A similar concern has been raised in the context of preclinical studies that involve implanting human-derived neural cells into other animals, raising the specter of creating nonhuman animals with human-like traits (Greene et al. 2005; Karpowicz et al. 2005; Greely et al. 2007).) The assumption that seems to underlie this concern—one which is generally not well supported by evidence—is that individual brain cells carry the traits we generally associate with entire persons: intelligence, personality, preferences, for example. Research suggests that, notwithstanding contributions from genetics (Wright 2005), these higher-order cognitive capacities emerge from networks of cells in the brain, not solely from an individual's genotype (Pascual-Leone et al. 2005; Sur and Rubenstein 2005). Because transplanted cells will generally be integrated into existing networks of cells, rather than reconstitute entire networks, it seems highly improbable that CBIs will cause recipients to acquire the cognitive characteristics of the cells' donors. Furthermore, early trials of CBIs are likely to involve non-neuronal cell types that are intended to produce missing or otherwise defective proteins or maintain the structural integrity of the CNS (Lazic and Barker 2003; Sanberg et al. 2005). Hence, we believe there is not good reason to expect that the implantation of disaggregated cells in the brain could so alter an individual as to make that person unrecognizable to his or her family members or friends.

Nonetheless, grafting cells might influence or modulate a network of cells in a way that results in more subtle changes in characteristics that the recipient regards as important to his or her sense of self. The extent to which any change is viewed as bearing on this sense of self may vary in individual cases, as different persons attach different levels of significance to their various traits. Moreover, whether a particular change is viewed as desirable or acceptable may depend on an individual's values and interests. For example, some aggressive persons might welcome the prospect of becoming more subdued, while others might fear that such a change would make them lose their "competitive edge."

Another concern is that a particular CBI might lead to a loss in function in parts of the brain, even where the intervention is successful in addressing the neurological disorder it is intended to repair. For example, if as a result of the intervention, neurons were "rewired" incorrectly, this could lead to the extinction or diminution of previously normal

capacities. Important autobiographical memories could be lost, facts could be forgotten, sexual desire increased or diminished, or one's affect altered. Related to such losses of function are a range of "abnormal" functional changes (e.g., seizures, neurogenic pain, dyskinesias), which, though not cognitive or behavioral in nature, could be disabling and problematic for those experiencing them.

Alternatively, a CBI could result in an enhancement, wherein gains in function exceed the therapeutic goal (Elliott 2003; Mehlman 2003; Greely 2006). The mechanism(s) by which such enhancement might be achieved are not clear at this point (Chatterjee 2004). It is not the case, for example, that increased neural proliferation would necessarily be beneficial. In fact, if not controlled, it is likely to be detrimental. Under certain conditions, however, it is conceivable that CBIs could modulate or enhance neural networks in a way that promotes more of the "right" kinds of connections between neurons or increased production of the "right" neurotransmitters, so as to have a net beneficial effect on cognition, mood, or behavior.

Importantly, there are at least two different scenarios in which enhancement could occur. The first involves an unintended improvement in function beyond expectations. For example, if a CBI for stroke not only repaired brain damage, but actually improved function in a localized region of the brain (e.g., a person's verbal fluency improved over baseline as a result of the intervention), this would represent an unintended enhancement, since the goal of the therapy was only to reverse damage caused by the stroke. In the second scenario, a CBI is delivered with the explicit intention of improving function above an individual's normal level of functioning, for example, improving memory or inducing a mood-enhancing effect in an individual with no underlying mood disorder. (A third kind of enhancement might aim at improving aspects of the person's functioning beyond the normal human range, but this seems likely to remain purely speculative for the foreseeable future.)

This distinction may prove to be artificial. However, we believe it is important to distinguish cases where enhancement is unintended, but possible, from cases where enhancement is the expressed goal of the intervention. To our knowledge, there are no serious efforts under way to use CBIs specifically to enhance neurological function in persons with no underlying disease or disorder. Regardless, concerns about intentional enhancement should not determine our thinking about the treatment of serious, often life-threatening neurological conditions in which enhancement might inadvertently occur. This is not to say that therapies under investigation could not possibly have enhancing effects. But the prospect of such enhancements does not justify constraining a promising line of medical research, nor does it justify withholding therapies from those who stand to benefit. (Similarly, the fact that stimulants such as methylphenidate (Ritalin, Novartis Pharmaceuticals) can enhance concentration and attention in healthy individuals does not imply that they should not be used to help individuals with attention deficit hyperactivity disorder.)

How Could Such Changes Occur?

Predicting the nature or likelihood of any changes in cognition, mood, or behavior at the outset of a clinical trial would be almost entirely speculative, but we propose that a number of factors might play influential roles in determining what functional changes might occur with CBIs. Of course, each proposed intervention or therapy is different and should be evaluated in light of its particular characteristics. Still, we believe there are at least five general factors that will be important to consider for all types of interventions, and could be profitably compared across interventions. First, the *genetic source* of the cells might prove relevant (Silani et al. 2004). Cells from an unrelated donor, for example, might induce changes that autologous cells would not induce. However, as noted previously, to the extent that higher-order brain functions emerge from cell networks—rather than genetic properties of the cells themselves—the source of the cells may be relatively unimportant for influencing changes in cognition, mood, or behavior. (The cell source could, however, have a significant adverse influence on the immune response to the transplanted cells.) Second, the *timing* of the intervention—either the subject/patient's stage of neurological development or the timing of the intervention relative to disease progression, including timing of the intervention relative to the onset of symptoms—might affect the degree to which cells engraft and differentiate *in vivo* (Escolar et al. 2005; Greene et al. 2005; Regenberget al. 2008); for example, neonates and children, whose brains are still developing, may experience more substantial integration of introduced cells than may adults with similar levels of neurological damage. Third, the *location* to which an intervention is delivered or targeted would presumably influence the types of changes one might expect to see (Greene et al. 2005). Cells injected in or around the spinal cord, for example, might result in changes in sensory or motor function (Modo et al. 2002; Keirstead et al. 2005), but not necessarily in cognition or behavior. Fourth, the *function* that cells assume would significantly influence the types of changes anticipated. Glial cells that promote remyelination and repair of the spinal cord would likely have different effects than, for example, cells used to repair damaged tissue in the cerebral cortex following stroke (Lindvall and Kokaia 2006). Lastly, the number of cells ultimately generated by the therapy, whether it requires one or multiple treatments, i.e., the degree of proliferation (and variables associated with proliferation, such as the density of new neural connections or the amount of a given neurotransmitter produced) could influence the magnitude of the changes we might expect (Goh et al. 2003). Overall, one might expect a local therapy in which cells are used as delivery vehicles for growth factors to entail a smaller risk for changes in cognition, mood, or behavior, whereas a global therapy involving cell replacement in the brain may represent a larger risk for such changes.

A WAY FORWARD

That we are unable at present to predict, let alone quantify, all of the risks of CBIs for neurological conditions is neither

reason to discount those risks nor reason to be deterred from responsibly designed and conducted research. But the lack of reliable data *is* reason to be candid about what is not known, so that as research proceeds, there is a clearer sense of the secondary research questions—most notably whether (and if so, how and to what extent) changes in cognition, mood, or behavior occur as a result of CBIs for neurological conditions.

Precisely because risks cannot be disclosed prospectively with adequate precision, potential subjects in studies of these interventions should be informed about the uncertainty that surrounds a broad range of potential unexpected side effects, including unintended changes in cognition, mood, and behavior. What is required is not the rehearsing of a lengthy list of possible effects but rather an explanation that helps potential subjects form a clear understanding that these interventions are still experimental, and that unintended changes could occur and, where appropriate, why in any particular trial there is reason to think that such changes are not expected. Particularly in trials where the subjects have serious neurological conditions, it is unlikely that a straightforward disclosure about the uncertainties surrounding possible cognitive or behavioral effects would deter many people from volunteering. But even if it did, it is essential to disclose this information in order to obtain valid informed consent.

As trials get under way, it will also be important to collect clinical data that bear on the question of whether changes in cognition, mood, or behavior occur, and if so, the precise nature and magnitude of those changes. We propose that, whenever feasible, subjects should undergo thorough neuropsychological testing before and at appropriate intervals after the intervention; furthermore, the same data should be collected prospectively on matched control patients, to account for changes that might be otherwise expected (Selnes et al. 2006). A standard battery of diagnostic tests, administered by a clinician skilled in their application, will be important for discerning and quantifying changes in cognition and describing whether or not they are stable after the intervention. Such tests could be augmented by additional instruments, such as the NEO Personality Inventory or a similar instrument that measures aspects of personality that are widely held to be stable across an (adult) individual's lifetime (Costa and McCrae 1992). Admittedly, establishing a meaningful baseline, defined by the subject's state at the beginning of the trial and prior to treatment, may be complicated when the subjects are infants or children; of course, this is only one of the concerns when including minors in CBI trials (Mathews et al. 2008), and one of many concerns in a larger debate about research with minors (Kodish 2005). The results of standardized neuropsychological and personality tests, when available, will provide valuable data on whether and to what extent clinically significant changes occur. Structured interviews with family and close friends of the patient pre- and post-intervention may also help identify perceived affective changes in subjects. Although we realize this information will never conclusively prove that particular types of changes do not or cannot occur, it will

nevertheless provide a point of reference for what types of changes it may be reasonable to anticipate.

CONCLUSION

Given the small but nonzero risk for unintended changes in cognition, mood, and behavior resulting from CBIs for neurological conditions, researchers conducting early human trials should consider the possibility of such changes in the risk-benefit analysis and in the consent process. Data from preclinical studies should be consulted, but are likely to be insufficient for identifying all of the relevant risks. Investigators should disclose the potential risks of unintended changes in neurological function as part of the informed consent process. Human subjects in clinical trials involving such CBIs should be monitored for changes in cognition, mood, and behavior to better identify and quantify these risks. This will require a pre-intervention evaluation as well as post-intervention evaluations at appropriate intervals, to discern whether changes are persistent or whether they resolve or intensify over time. Finally, when reporting research results, investigators should include information on adverse events, including any documented changes in cognition, mood, and behavior, as well as negative findings (i.e., instances in which no discernable effect is found) to further our understanding of CBIs for neurological conditions, including their risks and benefits. ■

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