Invasiveness is inevitable in psychiatric neurointerventions

Commentary on "They are Invasive in Different Ways": Stakeholders' Perceptions of the Invasiveness of Psychiatric Electroceutical Interventions. Bluhm et al., in press.

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In their recent target article, Bluhm et al. (2022) discuss the construct of "invasiveness" as it relates to medical treatments, and in particular to treatments that affect brain function. Crucially, they sought the views of stakeholders with different levels of involvement in electroceutical therapy. The key message of this work is that the term "(non)invasive" has different meanings to different people, and that experts must be careful to use this wording carefully, to be mindful of how a non-expert might interpret the term.

Routes to stimulating the brain

The term "non-invasive brain stimulation" (NIBS) is routinely used in lab settings to refer to methods that affect brain activity without the use of drugs or surgery. Bluhm et al. (2022) mention transcranial magnetic stimulation (TMS), but the term also extends to the use of electrical energy (e.g. transcranial direct or alternating current stimulation; tDCS, tACS), or ultrasound energy (transcranial functional ultrasound stimulation; tFUS). In each of these cases, the stimulation is applied to the head, and some of the energy released by the stimulator crosses the skull and other tissues, to affect cells in the cortex.

One definition of invasiveness refers to the spatial specificity of the intervention. Pharmaceuticals taken as tablets must run the gauntlet of the gastric system before being released into the bloodstream. Some fraction of the active compound works its way through the blood-brain barrier to affect neural tissue, leaving the rest to bind with whatever bodily tissues have the right structure. The gut contains receptors for neurotransmitters such as dopamine and serotonin, which explains why a common side-effect of neurological drugs is intestinal distress (Vaughan et al. 2000; Gershon and Tack 2007).

The apparent targeting of the brain means that NIBS approaches would seem to avoid this kind of side-effect. In Bluhm and colleagues' data, this notion of invasiveness is recognised both by a professional (*Psychiatrist_13*) and by a member of the public (*Public_11*), who said this: "I'd say medications [are more invasive] … because, they do get into your system rather than TMS is only working on your brain.". So the lay understanding of invasiveness aligns with the clinician's, and with the common usage in research settings.

Individual differences and turning up the dial

I and others have pointed out that the volume of tissue affected by NIBS extends beyond the target area (e.g. Davis and van Koningsbruggen 2013; Glannon 2015). The reason is pure physics. The tissues of the head vary in their conductance to electromagnetic energy. The skull, for example, is a stern insulator against electrical currents. This means that electrical approaches must either use a large current (as in ECT), or use clever positioning of the electrodes to direct as much energy as possible to the desired area of the brain. The effect of this insulation is that the electric field induced on the surface of the brain is 'blurred', having been filtered through layers of highly insulating and highly conductive tissue. Conversely these same tissues are effectively transparent to magnetic energy, meaning that TMS can be targeted more precisely. As a rule of thumb, a patch of cortex roughly 1 cm^2 in area is activated by TMS (Bungert et al. 2017), while in tDCS calculations show that a whole lobe of the brain may be stimulated (Huang et al. 2019).

The targeting of brain regions is further complicated by the fact that each person's brain shape is different, and it is not easy to locate a brain structure unless one also has an MRI image of the brain. A target brain area, say the angular gyrus of the parietal lobe which is involved in a number of cognitive processes, may differ between people in how deep it lies (the scalp-to-cortex distance), or in where it lies in the anterior-posterior or the dorsal-ventral axes (Davis 2021). This variance means that stimulation protocols tend to be dosed higher than required, to ensure that the target area is stimulated in all participants. This therefore means that in most participants the surrounding brain regions are also receiving a higher dose of stimulation, so exposing the participant to side-effects such as risk of seizure or altered cognitive function (Davis 2017).

Future developments in brain stimulation

Targeting of brain tissue is an import area of development in neuroscience. The diffuse electric field induced by tDCS and tACS means that a swathe of brain tissue is activated during stimulation, as the current travels from the positive to the negative electrode. One solution to this is to shape the electrode array. A single positive electrode placed over the target brain area, surrounded by a ring of negative electrodes, seems to focus the electric field around the target region, so avoiding off-target effects (Datta et al. 2009).

At present conventional NIBS, which is delivered to the scalp, is unable to target structures deep in the brain. To do so would require so much energy at the electrodes that the participant would likely experience painful heating or skin lesions, and the brain tissue closer to the surface may be damaged. Neuromodulation of regulatory structures such as the amygdala or the striatum would usually require pharmacological approaches (with the risk of side-effects) or deep brain stimulation (with the risks of brain surgery). An exciting recent development is the use of multiple, weak electric currents, that converge on the target area to produce an additive effect. Such temporally-interfering fields have been demonstrated in mouse brains (Grossman et al. 2017), and there is promising early data that suggest this modality may be feasible to stimulate midbrain structures in humans.

tFUS similarly uses the wave properties of the stimulation mode, in this case ultrasound, to focus energy within the head. tFUS is still early in its development, and requires a detailed image of the head to model how the ultrasound wave reflects around the skull (Arulpragasam et al. 2022). Nevertheless there have been some positive studies in healthy humans, and a limited number in people with neurological disorders (Darmani et al. 2022).

Reducing invasiveness will not remove it

Current trends in neuroscience are to increase focality of stimulation and to reduce off-target effects. If there is a spectrum of invasiveness (Glannon 2019), then this would seem to move the dial for electroceutical techniques. However it will never be practically possible to target stimulation precisely to a brain area using stimulation delivered from the scalp. The article by Bluhm and colleagues shows the importance of the construct of invasiveness to stakeholders at all levels of involvement, but importantly reveals that lay understanding of the term may be orthogonal to experts' notions, and that this confusion may bias a patient towards or away from an effective treatment. I suggest that the term "noninvasive" be avoided in public- and patient-facing communications.

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