

The basic idea

Hypothesis 1 *Let us suppose that psychiatric disorders are a consequence purely of 'brain configuration', and that treatment outcomes are consequences purely of the 'brain configuration' and the particular type of treatment administered.*

Terminology 2 *By 'brain configuration' I mean the particular way in which each neuron is connected by synapses to other neurons.*

The only way it gets any simpler is to assume that 'brain configuration' is of negligible significance, and already this picture is massively oversimplified compared to reality. Already, in this oversimplified scenario, an important question regarding Randomised Controlled Trials appears.

Terminology 3 *When I use the term **astronomical** for a number, I just mean 'very very big'. I don't need to go into order-of-magnitude estimates for much of what follows, since the complexity of the brain, and its possible configurations, let alone the complex way in which a single brain with a fixed configuration can respond to different nervous stimuli. (If you start working out the scale of the numbers, things on the order of $10^{1000000}$ and larger readily appear.)*

Now,

A brain consisting of 86 billion neurons and a few trillion synapses has an astronomical number of configurations. Of those, an astronomical subset of those configurations would result in a 'viable' human brain. Of that astronomical subset, a smaller, but still astronomical subset consist of brains that exhibit 'psychiatric disorders'. That astronomical set of brains exhibiting 'psychiatric disorders' is then categorised based on a few observable behaviours, into a total of 265 diagnoses. And if you share an astronomical number of these brain configurations between the 265 diagnoses of the DSM-5, naturally at least one diagnosis will contain an astronomical number of brain configurations, and likely all will.

One may counter that there are only about 7 billion human beings alive. The trouble is that, the next person born will not be one of these, and is not guaranteed to work the same way as the existing 7 billion. Basically the 7 billion living humans is an *extremely small* sample of the astronomical number of 'in principle possible' human beings, and if you want a theory that relates psychiatric symptoms to underlying aetiologies and treatment decisions, it is this space of 'possible human beings' that you are interested in. Without some means to rein in the massive complexity that results, with the approach of current Mental Health researchers relying mainly upon Randomised Controlled Trials with eligibility criteria essentially following the diagnostic categories of the DSM or ICD, and with a few chosen

treatment options trialled, it is extremely naive, if not hopelessly naive, to believe that such studies can yield reasonable results.

In *every* case where mathematical and statistical approaches are taken to study something where such an astronomical number of possibilities is present, *simplifying assumptions* are always necessary to give meaningful results, and the validity of the results is always contingent upon these assumptions at least approximately holding. This is what the term ‘model’ refers to in these circumstances. The degree to which a model pertains to reality is something to be ascertained empirically, and is not a given.

Question 4 *What simplifying assumptions are made in the mathematics and statistics used in psychiatric research? And what is the empirical and theoretical justification behind them?*

So naturally, within each diagnostic category, which I’ll refer to as a **group**, following the terminology of Feinstein[Fei01], there is, for at least some of the categories, an astronomical number of distinct brain configurations which exhibit these psychiatric disorders. In conducting Randomised Controlled Trials for drug treatments for one particular category amongst these disorders, it must surely be assumed **implicitly**, if not explicitly, that the qualitative differences in brain configuration (intra-group differences) between brains in a given category are of negligible significance.

Question 5 *If such an assumption is being made, either explicitly or implicitly, what is the empirical and theoretical justification? What are the consequences for the results if such assumptions hold approximately but not exactly? What are the consequences if they do not even approximately hold? In what way do real people deviate from these assumptions?*

Remark 6 *Why I have to leave this as open and vague as this is that I have yet to find any text or study where the assumptions are explicitly stated and justified.*

Let us consider that they are *not* assuming something along these lines. Suppose we have done an almost limitless number of RCTs on a single disorder, limitless so that ‘perfect meta-analyses’ can be conducted, and say ‘first episode of bipolar mania’ as an example diagnostic category, and suppose we have sufficient people meeting the same diagnostic criteria, and that RCTs of a number of drug treatments are properly conducted, with a placebo control group, and that there is a total absence of any kind of bias such as publication bias. What will the results tell us?

Now if it is *not* assumed that ‘differences in brain configuration within a diagnostic category contribute relatively little to the relationship between treatment choice and outcome’, what then? In this case, it is quite possible that the outcome of the treatment, on a per-brain-configuration basis, within each treatment group, can vary from the average by far more than the average of each treatment group, (and we are working here under the simplistic

assumption that all that matters is treatment choice and brain configuration, and there are reasons why that is incredibly simplistic).

Question 7 *So in the case that outcomes for individuals can differ from the average by significantly more than the average of one treatment group differs from the placebo group, then given a single individual meeting the eligibility criteria for the trial, **how much relevance do the results of the RCTs have to this particular individual?** That is, if you decide that the treatment that works best in the trial works best for this individual, solely on the basis of trial results, what are the chances that you are right? and what are the chances that you are wrong? And what are the consequences in each case?*

Closing remark

The above is extremely simplistic. But in proceeding from this simplistic viewpoint to actual reality, things are not going to get any simpler, and questions of the form presented above are not going to go away.

In writing this, it is hard to strike a balance between mathematical rigour of the kind which will make things unreadable to anybody without an academic background in a discipline such as mathematics, physics, computer science, or similar, and readability for a more general audience, intended to include those working in Mental Health. How can one simplify the above any further without losing the point?

And the point is roughly that mind and brain are too complex for the Randomised Controlled Trial-based approach of current mainstream Mental Health to yield reliable results, and that fixing this is not something that can be done with more trials, better trials, or a few meta-analyses. The assumption that there is a means to treat e.g. schizophrenia, which is: effective; common to all with schizophrenia; sufficiently good that it makes sense to go with this 'common treatment'; and that this means can be reliably empirically determined by Randomised Controlled Trials... this assumption is where I think things go badly wrong. The mainstream psychopharmacological psychiatry brigade have mistakenly assume the existence of a uniform solution to a problem which admits no such uniform solution.

This is why the *interactive* approaches of clinical psychology, and brief, but detailed formulation of a problem, and a per-person determination of which solutions and strategies work is so essential, as opposed to those which believe, on the basis of clinical trial evidence, that they know enough to pretty much take a look and dictate to a mental patient the right treatment.

References

[Fei01] A.R. Feinstein. *Principles of Medical Statistics*. CRC Press, 2001.