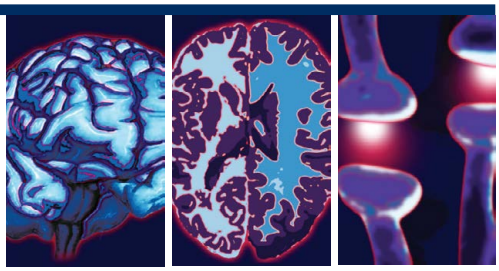
Letter To Editor



The Brain is the Same - Debate: On Significant but Unspecific Findings

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Abstract

There has been a remarkable constancy in the pathways of the brain over time and across species. The current gold standard for clinical investigation is the randomized controlled trial (RTC). Because of the unchanging nature of brain pathways and neuronal mechanisms, comparing an investigation or intervention group with a healthy or non-intervention control group as in RTC's lead to significant results that are often unspecific. For example, significant findings in pro-inflammatory markers for depression remain unspecific as long as they are not controlled against other mental or physical ailments-this is because the brain, which remains relatively unchanged, is unlikely to have a marker specific only for depression. It is also why non-specific interventions such as the placebo, exercise, mindfulness-based therapies result in nonspecific but tangible and effective results for a variety of medical conditions. In order to render significant findings more disease specific and clinically relevant, multi-arm trials that include several diseases or interventions are needed.

Keywords

Neuroscience, Human brain, Neuroanatomy, Neurotransmitters, Epigenetic programming

Discussion

We are learning from neuroscience that the human brain has stayed approximately the same for at least 20,000 years, despite the huge variety in existing phenotypes. This is true for genomics, epigenetic programming, and neuroanatomy, as well as hormonal responses along the stress axis and the high variety of neurotransmitters. For example, the neurotransmitters involved in stress response have a genetic sequence that can be traced back over 500 million years [1]. Our genetic coding is identical in 99% of humans and we share 98% of our coding with chimpanzees [2]. Almost 90% of any genetic variance occurs between individuals and not between ethnic groups [3]. The same is true for epigenetic mechanisms such as methylation and histone modification that do not change the sequence of the DNA but do change its expression in different environments [4]. Across both time and species, the hardware remains essentially unchanged.

In order to increase our knowledge of mental disorders that involve the human brain, the vast majority of molecular experiments, animal, clinical and social field studies are designed as controlled trials (RCT) as the gold standard in evidence-based medicine [5]. This set-up generates huge amounts of data with significant results, most of which are however unspecific. Controlling against healthy animals, healthy subjects, normal populations or standard environments produces results in the investigation arm that do not necessarily lead to specific insights into specific components of the investigated agencies. For example: significant findings in pro-inflammatory markers in depression will stay unspecific as long as they are not controlled against other mental or physical ailments [6]. As "the brain stays the same"

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it is rather unlikely that our brain is specific for depression only. The same is true for most other mental disorders and neurodegenerative ailments. According to Pubmed research (January 2017), less than 5% of over 600,000 controlled trials published follow the rationale of single controlled arm. If this ratio is roughly true, we constantly produce significant but rather unspecific results for the property investigated, leading to unspecific recommendations. This is not necessarily bad news. The placebo research of the last two decades demonstrated a powerful but rather unspecific intervention that runs through the same neuronal pathways (prefrontal cortex, amygdala, anterior cingulate cortex, insula) using the same neurotransmitters (gaba-erg, dopamine-erg, endorphins or cannabinoids) as powerful drugs do [7]. If that is by and large the case, then the recommendations remain relatively unspecific - or at least are no more specific than placebos - and in consequence do not allow us to gain a deeper and more specific and comprehensive understanding of our property under investigation. This is why non-pharmacological intervention and lifestyle changes (which are unspecific by nature) such as mindfulness-based therapies, exercise, nutrition, sleep hygiene, social support, and hydrotherapy lead to unspecific, but often tangible and effective results in a large variety of ailments and mental and physical disorders. In order to achieve specificity, further differentiations of the in-group investigation arm ("DIG") is required. This means: only if we start controlling for further in-group differentiation (arm 2 and 3, and more, see graph below) could we expect more specific results. If we refuse to undertake this procedure, we risk continuing to produce a lot of significant but unspecific results **(Figure 1)**.

At least three options can be concluded here. The first option is that we remain content with significant but unspecific empirical findings and interventions. This would support and feed into the general knowledge of highly significant but unspecific responses, which by and large

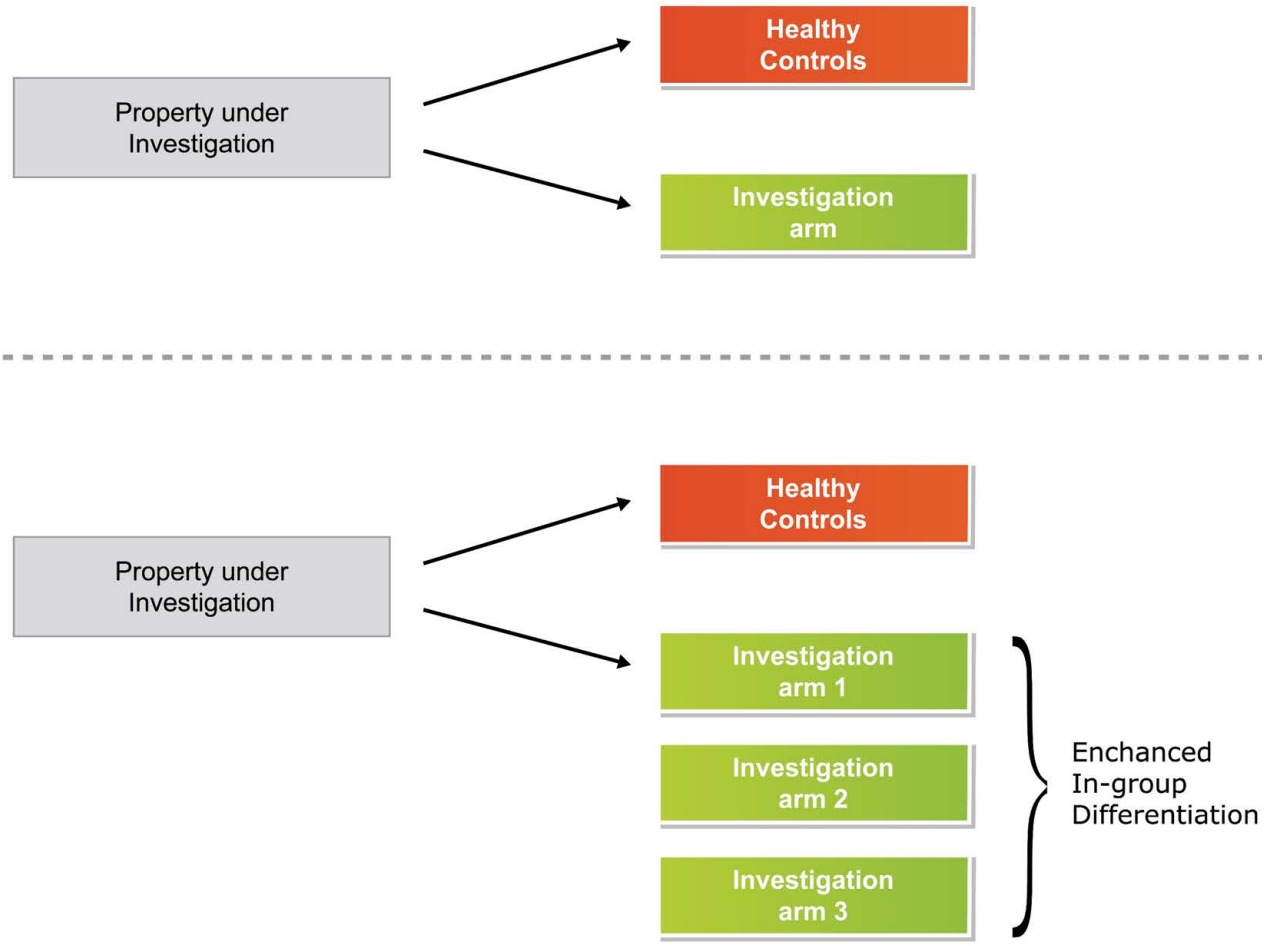

Figure 1: An enhanced differentiation within the investigation arm allows further differentiation of the property under research.

enhances placebo, but remains just as unspecific [8]. Second, we change the systematics in psychiatry (DSM 5) [9] towards fewer but more distinctive ailments and therefore fewer co-morbidities, which would make said ailments easier to investigate within an extended controlled design. Third, we change our standard methodological approach, considering further differentiations of the in-group within the investigation arm (‚DIG'), gaining more specific results. This means we start conducting more multi-arm controlled trials. The amount of specificity we intend to gain might eventually determine the clinical relevance we are looking for. The brain is complex and will very likely stay the same for the next hundred years, but the methods to explore it will hopefully not.

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