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European Journal of Integrative Medicine 6 (2014) 552–559

European Journal of INTEGRATIVE MEDICINE

www.elsevier.com/eujim

"Living is easy with eyes closed . . ." on blinded RCTs and specific and non-specific effects of complex therapeutic interventions☆

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Received 28 January 2014; received in revised form 20 June 2014; accepted 23 June 2014

Abstract

Introduction: It is assumed that, as measured during randomised placebo-controlled trials, specific and non-specific effects of an intervention do not interact with each other, and are simultaneously observable. It is argued this assumption means the results of RCTs (particularly for complex interventions, such as homoeopathy) are treated too simplistically.

Purpose of study: To examine if a complex intervention's specific effects and non-specific effects are complementary (in a sense derived and generalised from quantum theory), i.e., correlated sets of observables from an RCT, in which both are necessary to achieve a more complete understanding of the efficacy of an intervention.

Methods: Building on earlier work, and based on the properties of Abelian and non-Abelian algebras, a mathematical argument is developed, which is used to examine the nature of the relationship between a complex intervention's specific effects and non-specific effects as observables from RCTs.

Results: The mathematical argument suggests that it is essentially incorrect to assume specific effects and non-specific effects of a complex intervention (as measured during an RCT of a complex intervention) can be separated into simultaneously measurable, non-interacting sets of observables.

Conclusion: This calls into question not only the legitimacy of conclusions drawn from RCTs, but also the blinded observational stance of the RCT protocol (which currently justifies – and is justified by – a reductionist approach to the efficacy of complex therapeutic interventions). Indeed, such RCTs might well be demonstrating a Heisenberg-type uncertainty between the specific effects of the intervention and the non-specific effects of the consultation, as complementary observable parts making up a whole irreducible phenomenon: the therapeutic process.

Keywords: Evidence-based medicine; RCTs; Specific and non-specific effects; Complex interventions; Abelian and non-Abelian algebras; Quantum theory

Introduction

Evidence-based medicine and randomised placebo-controlled trials. As initially formulated evidence-based medicine (EBM) was "... an approach to health care that promotes the collection, interpretation, and integration of ... patient-reported, clinician-observed, and research-derived evidence (from randomised placebo-controlled trials – RCTs – author's emphasis).[1] The best available evidence, moderated by patient circumstances and preferences, is applied to improve the quality of clinical judgments" [1]. In other words, RCTs were envisaged as just one component of an evidence 'package', whose totality was to be derived from multiple sources [2].

Systematic reviews and meta-analyses of RCTs generally are now taken to represent the 'gold-standard' by which therapeutic interventions–conventional medical and complementary and alternative (CAM) – are judged scientifically acceptable. Other

☆ Lennon J, McCartney P, Harrison G. Strawberry Fields Forever. Lyrics ©Sony/ATV Music Publishing LLC.

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[1] Placebo-controlled studies test for specific effects, while comparative effectiveness trials do not try to isolate specific effects.

http://dx.doi.org/10.1016/j.eujim.2014.06.008
1876-3820/

forms of evidence and clinical decision-making tend to be either downgraded or ignored; a state of affairs criticised by Cartwright and Rawlins [3–6] who have pointed out the limitations of the RCT. Indeed, as Greenhalgh et al. point out, though EBM has had many benefits, it has also had some negative unintended consequences. While questioning whether the EBM movement is in crisis, they suggest it could be improved if EBM refocused on providing useable evidence that can be combined with context and professional clinical expertise so that individual patients get optimal treatment [7]. More trenchant responses have been elicited from clinicians, not only for EBM's overbearing attitude towards clinical decision-making [8], and perceived intolerance of 'therapeutic pluralism' [9] but also its underlying logical inconsistency [10].

EBM's effect has been to devalue (and in some cases ridicule [11]) interventions or procedures that do not lend themselves readily to the strictures of the RCT protocol (e.g., CAM therapies such as acupuncture, psychotherapy, physiotherapy, and homoeopathy). This, in turn, has led to questioning of the RCT protocol (e.g., by CAM practitioners) and how, in complex interventions [12], it might itself be a source of interference in the therapeutic process [13–15]. As the RCT is now perceived as the principal means by which an intervention's causal effects may be identified, it is important to ensure the RCT protocol is understood in greater depth so that optimal interpretation of its results may be achieved.

Because of the extreme attenuation of its remedies, homoeopathy has the added problem [16] of accounting for observed beneficial effects in trials [17,18] from within the currently accepted reductionist biomedical paradigm of drug action. For example, Brien et al. [19], reporting a 5-armed RCT of homoeopathy in the treatment of active relatively stable rheumatoid arthritis, concluded the positive benefits they found were due solely to contextual non-specific effects of the homoeopathy consultation; not to the specific effects of any individualised single or complex homoeopathic remedies (interestingly, others have pointed out that RCTs designed to observe the specific effects of homoeopathic remedies, say little about the non-specific effects of the consultation when the remedies are non-individualised, or report the disruption to the therapeutic process when the remedies are individualised [12,13]).

Complementarity in biomedicine? In coming to this conclusion, Brien et al. follow the general assumption that specific and non-specific effects of an intervention are separate observables of the RCT protocol, and as such, are considered not to interact or interfere with each other [20]. Here, we examine a different interpretation of the relationship between specific and non-specific effects of an intervention: that far from being separate and non-interacting, specific effects (SE) and non-specific effects (NSE) of complex interventions such as homoeopathy, as observed via the RCT protocol, may be complementary and incompatible with each other in a sense derived and generalised from quantum theory [21]. Such a quantum-like complementarity would mean that in studying the effects of the consultation, it might be difficult to observe simultaneously the pharmacological effects of the medications with the same degree of accuracy. On the other hand, if one were to concentrate on studying the pharmacological effects of medications, it might prove difficult to observe simultaneously the effects of the consultation with the same precision. Yet though incompatible, both sets of observations would be necessary in order to obtain a fuller description of the therapeutic process than either taken alone.

Complementarity is not unusual in biomedicine, e.g., in the sequence of normal pharmacological testing. First, pharmacological effects of medications are studied in phase I–III clinical trials, and only during phase IV trials can the general effects of normal practice be observed in post-marketing surveillance studies. Often the results appear incompatible; the case of antidepressants being a good example.

Thus, in normal practice, antidepressants (such as Prozac, aka Fluoxetine) have been regarded as effective medications [22]. Although their 'side effects' now cause concern (e.g., suicidal tendencies [23,24]), they have earned pharmaceutical companies large profits. However, except for severely depressed patients, the efficacy of antidepressants has been shown to be clinically insignificant against placebo [25]. In the case of severely depressed patients, their putative efficacy is thought to be due more to decreased responsiveness to placebo, than increased responsiveness to the antidepressant medication (Indeed, the pharmaceutical industry has expressed major concerns over the strength of placebo effects versus verum that has bedevilled clinical research into new antidepressants [26]. In addition, it has also been demonstrated in an RCT on the treatment of irritable bowel syndrome, that even when participants knew they were receiving placebo pills, they still got better [27]).

The example of antidepressants above highlights another kind of complementarity in the biomedical field: that of various methods that cannot be applied at the same time and need to be taken in sequence, the sequence being important. Thus (a) if a medication/procedure is studied first in clinical practice (e.g., because it has existed for a long time, such as many CAM complex interventions [28]), then the NSEs (in this case 'side-effects') in general practice are known from experience, and placebo-controlled RCTs are performed to determine the SEs. This is a completely different epistemological situation to (b) when a completely new medication is tested for SEs in RCTs and then only later on are its NSEs (i.e., 'side-effects') observed in general clinical practice. In the two situations (a) and (b), knowledge and outcome are completely different. A case in point here is the Cox2 inhibitors, e.g., Vioxx, which though efficacious were not broadly acceptable because of side effects brought to light in large observational studies [29]. Hence RCTs and observational studies may be considered complementary, and indeed, can complement each other.

Consequently, given what has already been said, if SEs and NSEs (as defined by the RCT protocol) were indeed complementary, then it would be necessary to reassess the meaning of the results of RCTs, particularly those performed on complex interventions. The purpose of this present paper therefore is to provide an argument for the complementarity of SEs and NSEs, and to examine its consequences for how the effectiveness of therapeutic procedures (particularly complex interventions such as homoeopathy) should be adjudged.

The RCT's implicit assumption, "Something rotten in the State of Denmark . . ."[2]?

Several limitations of the RCT have already been identified, including the difficulty in generalising from internal to external validity [3,6]. However, here we examine a different aspect: an implicit assumption inherent in RCT methodology that too could prove a limitation.

Weatherley-Jones et al. and others [12,13,30] and others alluded to this question while reviewing the placebo-controlled trial as a test of CAM and complex interventions. What was found was that within the RCT methodology is the assumption that SEs and NSEs of an intervention are treated as separate, non-interacting phenomena. The question then is, to what extent this implicit assumption is justified. The answer will be based on a mathematical argument concerning the difference between Abelian and non-Abelian groups, followed by a consideration of the implications of certain aspects of quantum theory, e.g., macroscopic complementarity and non-locality.

First though, it is interesting to couch the RCT's implicit assumption in algebraic terms. We shall call the verum arm of the trial A, and the placebo arm B:

A. The healing process during treatment (the verum arm of the trial) may be thought to consist of three elements which because it is assumed there is no interaction between them, they can be treated independently and purely additively:
(1) the natural course of the disease;
(2) the *non-specific effect* of the consultation, i.e., context;
(3) the *specific effect* of the treatment.
B. As a placebo is considered not to have any specific effects, then any effects in a placebo arm of a trial may be seen as due to the purely additive effect of:
(1) the natural course of the disease;
(2) the non-specific effect of the consultation/context.

The SE of the intervention can now be determined simply by subtracting the totality of B from the totality of A, i.e.,

$$\mathrm{A} - \mathrm{B} = (1 + 2 + 3) - (1 + 2) = 3$$

It should be emphasised here that this result is achieved because the various experimentally determined elements of A and B are assumed not to interact with or influence each other.

Method

Abelian and non-Abelian groups. In abstract algebra, an Abelian group (named after the Norwegian mathematician Niels Henrik Abel [31], is one in which the result of applying the group operation to two group elements is independent of their order. Under these circumstances, the group elements are said to commute. For example, Abelian groups generalise the well-known commutative arithmetic of integers under the operations of addition and multiplication, thus, $a + b = b + a$, and $a \times b = b \times a$. This can be generalised as

$$a * b = b * a \quad \text{or} \quad a * b - b * a = 0$$

where the symbol '*' represents the group operation. In this sense, the treatment of the various elements of trial arms A and B above may be said to be Abelian.

A non-Abelian group, on the other hand, is one in which there are at least two elements a and b such that applying the group operation [32] is dependent on their order, i.e., $a * b \neq b * a$ or $a * b - b * a \neq 0$.

Such groups are said to be non-commutative. Now processes generally consist of a series of operations or actions whose order matters, leading to different observable outcomes depending on what order those operations are performed. A trivial example is the process of bread making. Here, the sequence of 'operations' involved include (a) mixing flour, water, yeast and other ingredients; (b) kneading these ingredients into a dough; (c) allowing the dough to rise, and (d) baking the risen dough. Changing this operational sequence is the difference between an observably wholesome tasty loaf of bread, and something inedible. Thus, the process of bread making might be considered non-Abelian: the order of operations matters in producing the desired result – an edible loaf.

Important examples of the practical application of non-Abelian algebras [33] are in engineering, chemistry, and physics, particularly in the latter for the modelling of quantum phenomena. Thus, Heisenberg showed [34] that it is impossible to measure simultaneously and measure with the same high degree of accuracy observables such as position and moment of a quantum system. Indeed, the more accurately one knows the position of a quantum system, the less accurately one could know its momentum, and vice versa. A similar relationship exists for quantum systems between the measurement of energy and time.

Complementarity. Such observables are said to be conjugate or complementary, and the algebra required to describe them is non-commuting (and therefore non-Abelian). In the case of orthodox quantum theory, the extent to which this algebra does not commute depends on the universal number Planck's constant h multiplied by $i = \sqrt{-1}$, and divided by 2π [34]. So if a and b are two complementary observables of a quantum system, then, $a * b - b * a = ih/2\pi$.

The notion of complementary observables in quantum theory [35] was first enunciated by the Danish physicist Niels Bohr in 1928. For example, depending on the experimental set-up, the observed behaviour of light and subatomic particles is found to be sometimes wavelike, sometimes particle-like (i.e., photons, electrons, atoms and even whole molecules express wave-particle duality). It is impossible, however to observe both the wave and particle aspects of such phenomena simultaneously, but together they present a more complete description of quantum phenomena than either of the two taken alone [36].

Non-locality and quantum entanglement. Complementarity is also a pre-condition for quantum entanglement, predicted by Schrödinger in 1935. Multi-component quantum systems sometimes cannot be described classically in terms of the sum of their localised independent parts, but have to be described as

[2] Hamlet, Prince of Denmark, by Shakespeare W. Act 1, Scene 4; Marcellus to Horatio.

one single non-localised system until measured, even after the parts have interacted and separated. Under these circumstances, the results of measurements carried out on two or more of the seemingly separate subsystems show instantaneous acausal correlations with each other [37].

Non-locality has been defined as "the mysterious ability of nature to enforce correlations between separated but entangled parts of a quantum system that are out of speed-of-light contact; to reach instantaneously across vast spatial distances or even across time itself, to ensure that the parts of a quantum system are made to match" [38]. This is sometimes known as Einstein–Rosen–Podolsky or EPR entanglement after the three scientists who tried to demonstrate the incompleteness of quantum mechanics [39]. Essentially, they argued that as nothing in the universe travels faster than light, the separate parts of an entangled quantum system could not possibly be instantaneously connected, as this would violate the relativistic upper limit on the speed of propagation of information. Einstein famously called this "spooky action at a distance".

Thirty years later, conditions were discovered for the localised parts of a quantum system to be classically independent of each other (known as Bell's inequalities) [40]. This made it possible to test experimentally whether the parts of a quantum system were entangled as predicted by quantum mechanics. If Bell's inequalities are violated, then non-locality has to be the only logical conclusion; something that has now been experimentally verified many times, most famously by Aspect et al. [41].

This undermines the centuries-old classically deterministic picture of the universe. Only later was it realised that what scientists had actually done was to exchange a physical theory about the universe itself for one that dealt with what could be known about the universe. In other words, human experience, knowledge, and its limitations have now to be factored into fundamental theories about the universe.

Finally, it is necessary to point out that quantum physics is also inherently statistical. Thus, the observed measured outcome of an experiment will generally not be the same if the experiment is repeated several times. Only the statistical mean of the observed measured values, averaged over a large number of runs of the experiment, is a repeatable quantity. Quantum theory does not predict the result of individual measurements, only their statistical mean. This predicted mean is called the expectation value, and importantly, is represented not by a number but by a linear mathematical operator.[3]

Generalisation of complementarity and quantum entanglement. Standard models of how science is done usually presuppose some tacit or implicit assumptions [42,43]. Walach and von Stillfried have further pointed out that, "... while questions that arise within a paradigmatic framework can be discussed and debated using accepted methodology that can decide between competing alternatives, for instance through an experiment, this is not always possible when it comes to decide between different paradigmatic frameworks. Often the presuppositions needed for the alternative framework question the presuppositions of the old methodology ..." [42].

Because the generally accepted scientific paradigm tends to be local, reductionist, and causal, it consists of a set of assumptions about reality that not only have difficulty accommodating holistic structures and relationships, they are not geared towards incorporating non-local (acausal) correlations, e.g., complementarity and quantum entanglement. Only orthodox quantum theory achieves this, but its formalism and mathematical structure confine it to the microscopic domain of sub-atomic, atomic, and molecular entities and interactions.[4]

Notions of complementarity and entanglement however, can have implications far beyond the specific meaning ascribed to them by orthodox quantum theory. Thus, examples have been cited from engineering and the cognitive sciences, especially psychology [21,44,45]. Here, perhaps one of the most profound applications of complementarity and entanglement explored outside of orthodox quantum theory (by Jung and Pauli [46]) concerns the relationship between mind and matter, or more precisely, the mental and material observables of a system. In considering complementarity and entanglement outside of its usual physical context, attempts have been made to apply orthodox quantum theory directly to the problem [47,48]. An altogether more radical approach however, was taken by Atmanspacher et al. [44]. While maintaining orthodox quantum theory's mathematical structure, they generalised its theoretical framework by relaxing those conditions that keep it restricted to the microscopic domain, so that complementarity and entanglement can become useful concepts in much broader contexts. This more generalised, relaxed version of ordinary quantum theory, originally known as weak quantum theory (WQT), is now called generalised quantum theory (GQT) [21,42,49]. Generalised entanglement has for example been applied to psychosocial, paranormal, and complementary medical phenomena for which classical (i.e., direct causal) explanations could not be found. Thus, GQT shares with orthodox quantum theory complementarity and non-commutability of observables. Also in GQT, as with orthodox quantum theory, holistic correlations and entanglement arise if in systems consisting of many parts, observables pertaining to the whole system are incompatible with observables of its parts. GQT, however, differs fundamentally from orthodox quantum theory in three ways.

1. First, complementarity and entanglement are not restricted to a particular degree of non-commutability of observables. In other words, there is no constant in GQT like Planck's constant h, and the equation $a * b - b * a = ih/2\pi$ (which confines orthodox quantum theory to nanoscopic domains) no longer

[3] Linear operators cannot be assumed to behave like ordinary numbers. If observables cannot be measured simultaneously, then the linear operators representing them will not commute; something that is not allowed for in classical mechanics, but is the basis of the mathematical formulation of quantum mechanics.

[4] This is because the degree to which the algebra of orthodox quantum theory does not commute is bounded by the very small number Planck's constant $h = 6.63 \times 10^{-34}$ Js.

holds. Rather, this equation generalises to $a*b-b*a=iC$, so that the degree of non-commutability C will vary from case to case.

2. Second, GQT has no interpretation in terms of probabilities, as does orthodox quantum theory, and expectation values (i.e., the mean value of a series of determinations of an observable represented not as a number, but as a linear operator) [50] are if anything non-linear.
3. Third, in GQT it is not possible to argue that complementarity and indeterminacy are of ontological,[5] rather than of epistemological[6] origin as one can in orthodox quantum theory. Indeed, in GQT, it is much easier to argue that incomplete knowledge of a system or perturbations caused by observation are epistemological, not ontological reasons for complementarity and indeterminacy.

Finally, it should be noted that, from the point of view of the theory of categories (i.e., the "mathematics of mathematics") [51], GQT is a more basic and general theoretical description of nature than is orthodox quantum mechanics: indeed, the latter may be regarded as a special case of GQT. Thus, GQT and other metaphorical applications of quantum theory mentioned here [13,20,52,53] effectively free complementarity and non-local entanglement from their confinement within the microscopic domain of atomic and sub-atomic physics, to find more formal recognition in our everyday macroscopic world. How these insights can be used to describe the effects of RCTs on the therapeutic process concerns the rest of this paper.

Results and interpretation

As a 'complex' intervention is by definition one with multiply interacting components and non-linear causal pathways [54], then the assumption that specific and non-specific effects of an intervention can be treated as separate, non-interacting phenomena is, most likely, an over-simplification. One might ask therefore, what the effects might be of specific and non-specific effects being non-Abelian and complementary.

While investigating double-blinded homoeopathic pathogenic trials (aka 'provings'), Walach et al. [14,55] noticed that test subjects reported homoeopathic remedies (even at ultra-high dilutions beyond Avogadro's Number) produced more symptoms typical for a specific remedy than non-typical symptoms. Intriguingly, however, these workers also observed a non-classical pattern where symptoms of a remedy in the verum arm of the trial appeared to be mimicked to a lesser degree in the placebo arm [56].

Interestingly, there has been some confirmation of this observation by another research group [57], which suggests a form of non-local entanglement between the trial arms, such that information is shared between them. Certainly, such entanglement as a direct result of RCTs' blinded protocol has previously been considered [13,14,20,44,52–54,58–60], in which case, treating specific and non-specific effects of an intervention as independent of each other – i.e., as Abelian – would at the very least be questionable, especially as it is clear that non-specific effects play a significant role in the healing process [61,62].

Indeed, separation of the therapeutic process into SEs and NSEs might be seen, by its very nature, to be an artefact of the RCT methodology, as in real life, there is no such separation. Random allocation of an intervention (verum) and placebo (to rule out practitioner or patient bias) is not how complex – or indeed any other – interventions are practiced in real life. Here, ideally a (contextual) therapeutic relationship develops between the practitioner and patient, such that both tend to know what is happening during the session. On the other hand, the blinding inherent in the RCT protocol generates a situation in which ultimately patient and practitioner know that they do not know what is happening. This could inadvertently affect the development of a therapeutic context, with a concomitant impact on the effect sizes of interventions [63]. Significantly for the thesis put forward in this paper, Lund et al. note that, "The most important implication of the finding that drug effects and placebo effects are less than additive is that the drug effect can probably not be estimated by subtracting the placebo response from the total treatment effect in RCTs" [64].

This brings us back to the 5-armed trial by Brien et al. [19] mentioned earlier, in which the observed clinical benefits of homoeopathic treatment in patients with active yet stable rheumatoid arthritis, were ascribed solely to the non-specific contextual effects of the consultation, not to the specific effects of any homoeopathic remedies. The authors concluded, "Given the magnitude of these effects and the lack of reported side effects, the impact of the homoeopathic consultation is of clinical relevance to patients and clinicians alike". Support [65] for this partial 'endorsement' of homoeopathy asserted Brien et al.'s results should be taken at 'face value', i.e., any beneficial effects are due to the consultation not to any homoeopathic remedies, which in any case were dismissed as implausible and ineffective.

Such a conclusion is premature for several reasons. First, the trial was seriously underpowered in several of its key arms concerning the use of (individualised and complex) homoeopathic remedies [20]. Brien et al. therefore were in no position to claim whether or not homoeopathic remedies in their trial produce any specific effects. Also, by considering the homoeopathic consultation as a non-specific effect, these authors ignore the possible specific effect of the remedy matching process, peculiar to homoeopathy [66]. Nevertheless (and contrary to Weatherley-Jones et al. [12] and what is being proposed here), Brien et al. assume SEs and NSEs are separate and non-interacting and so may be treated as Abelian.

Given what has been discussed earlier and findings from other RCTs, there is an alternative interpretation of Brien et al.'s results: that what is being observed is complementarity between SEs and NSEs of the intervention, so they would have to be treated as non-Abelian.

Thus, Brien et al. claim they found no clear differences in their RCT due to homoeopathic remedy type (be it complex or individualised), while observing beneficial non-specific effects

[5] i.e., they belong to the *very nature of the system* and cannot be decomposed by refinement of observation.

[6] i.e., what can be *known about the system* by observation.

of the consultation. It is possible that by concentrating observation on the contextual NSEs, this coincided with an increased uncertainty in observing what the SEs of the remedies might have been. In contrast however, and as Weatherley-Jones et al. [12] have pointed out, concentrating observation on the SEs of homoeopathic remedies in RCTs, seems to lead to an increased uncertainty in observation of the NSEs of the consultation. If this point of view is correct, then SEs and NSEs could well constitute a pair of complementary observables.

Conclusion

If SEs and NSEs are assumed to be members of an Abelian group, then under the group operation of addition, they would commute. As has already been explained this would facilitate drawing conclusions about the SEs of an intervention from the results of an RCT, simply by subtracting the results of the placebo arm of the trial from those of the verum arm.

This assumption has been questioned [63,64]. Indeed, if the RCT is considered as a process consisting of a series of operations, then the order in which they are performed will most certainly matter. Consequently, this means the relationship between RCTs' observables – SEs and NSEs – should be considered not as independent, commuting and Abelian, but as complementary, non-commuting and non-Abelian.

Contrary to Brien et al., therefore, this suggests that RCTs which attempt to isolate the effect of the medicine, seem to lose sight of the consultation, while RCTs that attempt to isolate the effect of the consultation seem to lose sight of the medicine. It is this that resonates with the complementarity inherent in orthodox quantum theory, but more particularly with generalised quantum theory, and its ability to expand the use and meaning of this term beyond the realms of the microscopic [67]. Indeed, what RCTs of complex interventions might well be demonstrating is that we can know about the therapeutic intervention or the consultation as parts of a complementary pair of phenomena making up a whole, but we cannot know both with equal certainty at the same time; in essence, a biomedical restatement of Heisenberg's Uncertainty Principle[7] for the therapeutic process.

Of course (as postulated by GQT and quantum theoretical metaphors of the therapeutic process), the degree of uncertainty here would not be anywhere near as mathematically precise as that predicted by the orthodox quantum theory of the microscopic world, and moreover would most probably vary from case to case. More experiments will need to be performed however, before any such biomedical version of Heisenberg's Uncertainty Principle could be confirmed, but if it were, it would be as a direct consequence of the non-commuting, non-Abelian complementarity of SEs and NSEs postulated in this paper.

[7] Heisenberg's Uncertainty Principle, articulated (1927) by the German physicist Werner Heisenberg, states that the position and the velocity of an object cannot both be measured exactly, at the same time, even in theory. The very concepts of exact position and exact velocity together, in fact, have no meaning in nature.

One can now begin to appreciate how the over-simplifying assumption of SEs and NSEs being independent 'simultaneously measurable' observables, appears to make it easier to judge the efficacy of complex therapeutic interventions. But this now raises an interesting possibility. The epistemological separation of observables from an intervention into SEs and NSEs and their subsequent complementarity, could be the result of how we choose to observe a whole, integrated, irreducible, real-life phenomenon (aka, the therapeutic process) through the limiting reductionist prism of the blinded RCT protocol. If so, then this indicates a fundamental limitation (along with reservations about the primacy of the RCT made by Cartwright and Rawlins [3–6], and distortions of the EBM 'brand' [7]), which further questions the blinded RCT as THE 'gold standard' testing procedure, especially for measuring the efficacy of complex therapeutic interventions.

Conflict of interest

The author declares that there is no conflict of interest.

Acknowledgements

The author thanks Ms. Rachel Roberts, Dr. Alex Tournier, and the other organisers of the first HRI Conference in Barcelona 2013, for the many helpful discussions that event inspired, which ultimately led to the preparation of this manuscript.

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