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ORIGINAL PAPER

First evidence of Beauvais' hypothesis in a plant model

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Introduction: **Beauvais presented the application of a so-called 'quantum-like model of homeopathy' by introducing the idea of a type of randomization/unblinding which he called '*in situ*'. He predicted that randomized studies based on this type of randomization/unblinding lead to more pronounced effects in placebo controlled randomized homeopathic trials. We designed an experiment regarding wheat germination and stalk length to investigate Beauvais' idea of '*in situ* randomization/unblinding' using a homeopathic dilution of sulphur (LM VI) as compared to placebo as well as to water.**
Aim and method: **The primary aim of this double-blind randomized controlled experiment was to investigate whether there are differences of '*in situ* randomization/unblinding' vs 'central randomization/unblinding' with respect to the effect of a homeopathic substance compared to placebo. The secondary aim of our study was to examine possible differences between the sulphur and the placebo group in the '*in situ*' arm regarding germination and/or stalk growth of wheat seedlings measured after a seven days exposure. Wheat was treated either with sulphur LM VI, placebo, or water. The wheat grains were placed on glass lids and treatment was performed following the '*in situ* randomization/unblinding' as well as 'central randomization/unblinding' method. Germination was measured and classified into three categories.**
Results: **Under '*in situ*' randomization/unblinding the odds of a seed not to germinate is 40% lower if treated with sulphur compared to placebo ($p = 0.004$). In contrast, these odds are practically equal in the 'central' meta-group (OR = 1.01, $p = 0.954$). Under '*in situ*' randomization/unblinding the odds of a seed to germinate with a length ≥1 mm is practically equal if treated with sulphur or with placebo (OR = 0.96, $p = 0.717$). In contrast, these odds are 21% higher under sulphur compared to placebo in the 'central' meta-group (OR = 1.21, $p = 0.062$). In summary, we found a sulphur effect that is significantly different between '*in situ*' and 'central' randomization/unblinding relating to all three stages of germination.** *Homeopathy* (2016) **105**, 270–279.

Keywords: Beauvais' hypothesis; Quantum-like model of homeopathy; Plant model; Wheat; Sulphur; *In situ* randomization/unblinding; Central randomization/unblinding

Introduction

The gold standard for assessing the efficacy of a medical treatment is the randomized controlled trial (RCT).[1] In his paper of 2013, Beauvais presented the application of a so-called 'quantum-like model of homeopathy' by introducing the idea of a type of randomization/unblinding which he called '*in situ*'.[2] He predicted that randomized

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studies based on this type of randomization/unblinding lead to more pronounced effects in placebo controlled randomized homeopathic trials.

In the past, randomized, blinded and placebo-controlled homeopathic studies were often unable to establish the evidence of an isolated effect, as opposed to randomized, but open comparisons.[3] Randomization and blinding are hypothesized to lead to an entanglement situation between homeopathy and the placebo group. Thus the effects between the groups are 'smeared', i.e. specific effects of the homeopathic medicine occur also in the placebo group. Beauvais' theoretical model assumes that a randomized, blinded, placebo-controlled study is formally analogous to a 'single-particle interferometer', a device demonstrating the quantum nature of photons. The special feature of the interferometer is that through mirrors and beam splitters the photon is not measured on its path, so it can spread as a wave. This is even the case if only one photon is sent through the apparatus, meaning a photon is travelling as a wave on two paths.[4] At the end an interference pattern is produced by the last mirror and the two wave components go into two detectors via a constructive and destructive interference, respectively.

According to Beauvais, a clinical situation ('open-label trial') in which the homeopath and the patient know which drug is prescribed is similar to the situation in which the photon is travelling as a wave. The hypothesised reason is that there is no external ('central') supervisor, who determines and controls the process from outside. The superposition is not prevented and a possible entanglement remains preserved. The situation of a randomized and blinded clinical trial, however, is comparable to the situation when a so-called 'which-path-measurement' is made.

In the interferometer analogy the probability wave collapses into a defined particle, meaning that the photons behave as particles. In accordance with the formalism they take either one or the other path and end up on the mirror devices again either in the one or in the other detector, with equal probability of one half. The superposition and the wave character disappear and the particle character emerges. A randomized, blinded clinical study ('centralized blinded RCT') is hypothesised to be an analogous case: it forces the system of patient, practitioner and remedy into a causal frame with the result that the probability of finding an effect is one half[2]: it shows up in the placebo or in the active treatment arm with equal probability.[5]

To meet these challenges Beauvais proposed to perform randomization and unblinding as close as possible to the patient as follows: randomization is done by the prescribing physician on the spot ('*in situ*') and, after the treatment period and directly after measuring the clinical outcome, to unblind it to both, the patient and the practitioner. This approach is contrary to the common conduct of clinical studies where randomization is done by a central institution or person and unblinding takes place for the whole data set after the data of all patients have been entered into a data base.

The considerations of Beauvais may be compared with those of Milgrom.[6,7] There, the importance of (double-) blinding in RCTs is also stressed. A quantum-like formalism that includes entanglement is proposed, the double-slit experiment being used as illustrative example. In the case of RCTs, macroentanglement should be considered. Then, the quantum mechanical formalism is used in a metaphorical way[6] or in the form of generalized quantum theory.[7]

Two kinds of entanglements are considered by Milgrom: PPR entanglement (between the patient, practitioner and remedy) and that between verum and placebo. Interestingly, the blinding procedure (partly) destroys the PPR entanglement, whereas it establishes verum-placebo entanglement. Then, verum and placebo effects do not differ significantly from one another.

This may be compared with Beauvais. Instead of PPR entanglement, the cognitive state of the couple patient/practitioner is considered, but not explained in detail. In principle, this cognitive state is able to interfere with itself (corresponding to entanglement). Usual central randomisation, however, destroys this superposition. At the same time, verum and placebo effects become similar or identical, which is called 'smearing effect' by Beauvais.

Even if the model of Beauvais is not sophisticated enough to explain all results of experiments or trials, he makes a concrete proposal concerning a new mode of randomisation ('*in situ*'). It can easily be tested whether this increases the efficacy of homeopathic treatment. The present paper tries to investigate Beauvais' theory in an experimental setting.

For our present study we chose a plant model for the homeopathic basic research experiment to test Beauvais' hypothesis. The testable prediction is that the difference between placebo and homeopathic remedy vanishes in centralized blind trials due to 'smearing' (i.e. specific effects occurring in the placebo group), while 'smearing' is avoided by *in situ* randomization/unblinding. In the '*in situ*' setting, it is a prerequisite that the treatment allocation is done in a locally defined order (*in situ* randomization) and that the results are recorded in an unalterable way before locally unblinding the allocated treatment. As already stated by Atmanspacher,[8] further developed by Walach[9] and by Milgrom,[10] it is expected that non-local factors will lead to resistance to reproducibility due to counterintuitive phenomena and a quantum entanglement.[11]

Almirantis even hypothesizes that 'significance' conveys to cell cultures, plants and physiochemical systems.[12] Based on all these considerations, our idea was to develop a laboratory experiment for plants. This experiment includes the possibility to directly compare Beauvais' '*in situ* randomization/unblinding' with the common 'central' way. The three groups to be compared within each form of randomization/unblinding are homeopathic medicine (globules of sulphur LM VI) plus Volvic water (as nutrient solvent), a control substance (placebo globules) plus Volvic water (as nutrient solvent), and Volvic water alone.

We designed an experiment regarding wheat germination and stalk length to investigate Beauvais' idea of '*in situ* randomization/unblinding' using a homeopathic dilution of sulphur (LM VI) as compared to placebo as well

as to water. The primary aim of this double-blind randomized controlled trial was to investigate whether there are differences of '*in situ* randomization/unblinding' vs 'central randomization/unblinding' with respect to the effect of a homeopathic substance compared to placebo. The secondary aim of our study was to examine possible differences between the sulphur and the placebo group in the '*in situ*' arm regarding germination and/or stalk growth of wheat seedlings measured after a seven days exposure.

Materials and methods

Materials

The experiments are carried out on grains of wheat (*Triticum aestivum*). The species of wheat was Cultivar Florida harvested in 2007 (Leibniz Institute of Plant Genetics and Crop Plant Research (IPK), Gatersleben, Germany). The wheat used for this experiment is weakened by natural means. This is achieved by prolonged storage for 7 years in this case.[13]

Materials used for the experiments were Volvic water (Volvic® Water, Danone Waters Deutschland GmbH, Frankfurt, Germany) as nutrient solution; 60% ethanol (Laborchemie Apolda GmbH, Apolda, Germany) for pretreatment of wheat; homeopathic remedy sulphur LM VI globules size 1, and placebo globules size 1 (both Remedia, Eisenstadt, Austria), prepared according to HAB 2011 (Homöopathisches Arzneibuch; Homeopathic Pharmacopoeia, HV 10, Germany). The laboratory material consists of latex powder free examination gloves (MediQuick, Osnabrück, Germany) and a latex-free face mask (Kimberly Clark, Koblenz-Rheinhafen, Germany) avoiding contamination of the test material; sterile polystyrene tweezers (MediQuick) to place the wheat for cultivation on the upside down placed glass lid of a glass jar (1000 mL volume; J. Weck GmbH u. Co. KG, Wehr, Germany); filter paper (Whatman N° 1, cellulose, 90 mm diameter, grade 2; Whatman, Dassel, Germany) as mat for the wheat on the lid; a pipette (Eppendorf Research plus®, 500−5000 μl; Eppendorf AG, Hamburg, Germany) and pipette tips (Eppendorf epT.I.P.S.®, Eppendorf AG) for applying the culture medium; and aluminium bags (A 30 T; Long Life for Art, Eichstetten, Germany) to cover the jars.

Screening of homeopathic substances

The selection of homeopathic substance for the later main experiment (sulphur LM VI) was based on symptoms of the grains analogous to selection in patients. Medical treatment with homeopathic potencies can be of great interest to organic agriculture since this way of treatment relies upon natural substances and inherent self-regulation principles. Treating plant diseases relies on the strictly phenomenological simile-rule of homoeopathy. This rule states that the substance, which in a healthy organism produces symptoms that correspond most to those of a particular sick organism, is chosen as homoeopathic remedy in potentised form.[14]

Since a 'Materia Medica' for plants − a compilation of symptoms which plants show after poisoning with a given substance − does not currently exist, ways to approximate classical homeopathy may be the use of phenomenological or biochemical symptoms on basis of the simile principle.[15] For this purpose homeopathic rules were applied and copied to the plant model. One of the authors described symptoms (KT) while another author experienced in classical homeopathy (MF) collected the symptoms and

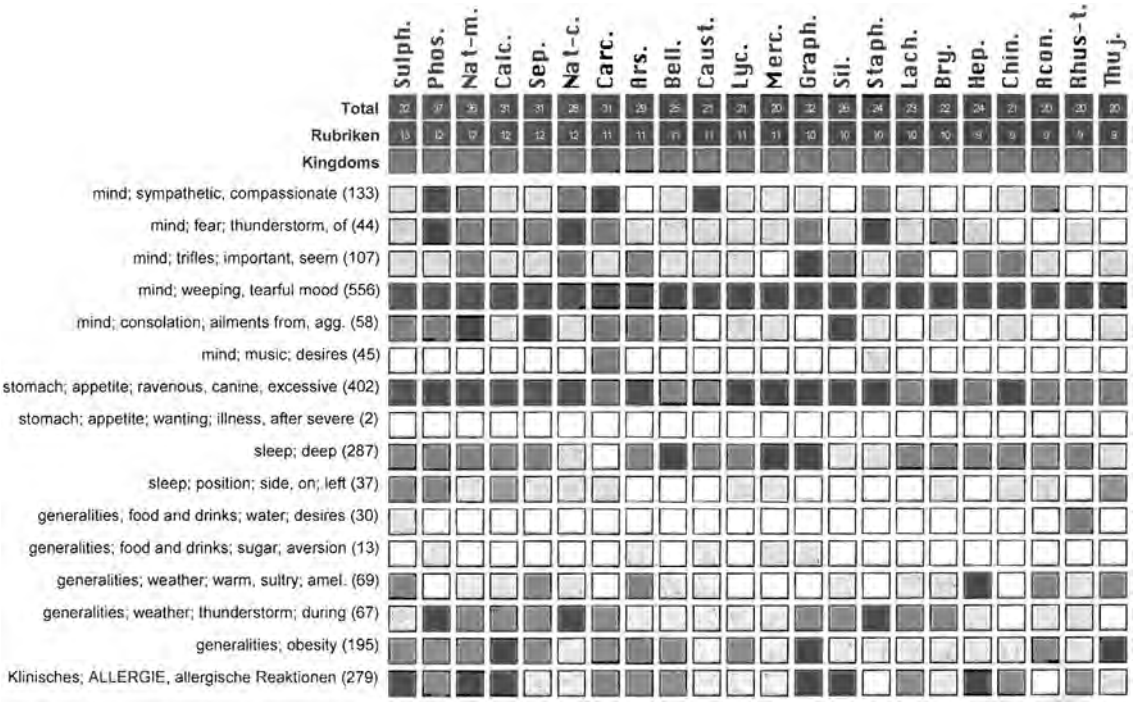

Figure 1 Repertorisation after anamnesis.

performed repertorisation (McRepertory Version 8, Synergy Homeopathic, Novato, CA, USA) extrapolating plant symptoms analogous to human symptoms (Figure 1). Biological symptoms like abiotic stress factors such as extreme temperatures, water availability, high salt, sucrose, and deficiencies or toxicity of minerals, which severely affect the germination of wheat,[16] were compared with the homeopathic Materia Medica. Increasing concentrations of sucrose e.g. revealed decline of growth,[17] excessive supply of water leads to oxygen deficiency[16] and is not accepted by plants and/or leads to its death. After having repertorised all symptoms, three remedies appeared to fit with high probability: sulphur, phosphorus and natrium muriaticum (=natrium chloratum).

The next task was to discover the appropriate potency. To gain information on consistency of homeopathic preparations and thus on the reproducibility of the experiments, additional tests prior to the main experiments were completed. The first preliminary tests were carried out in a randomized and unblinded manner. The selected potency was 200c followed by tests using LM VI for all three substances. The selection of 200c and LM VI was based on the assumption that plants demonstrate a very good receptiveness on high dilutions.[18] In addition, the test substances were original globules, which are also administered to humans.

We used globules instead of dilutions in order to avoid toxic effects of ethanol on wheat. Since globules are impregnated with an ethanol-water mixture, the experiments were as close as possible to usage in humans. Preparations without ethanol might not have yielded the same results.[19] Homeopathic globules consist of saccharose which might negatively affect germination and growth of grains. This has already been confirmed in earlier experiments at the same institution (unpublished data). In these experiments it was detected that one globule is the maximum to be added to 20 grains in 5 mL of a nutrient solution without exhibiting negative effects of saccharose in the experiment (unpublished data).

The nutrient solution for all three groups consists of Volvic water. The contents of Volvic water is as follows: calcium 12 mg/l, chloride 15 mg/l, sodium 12 mg/l, potassium 6 mg/l, silicium 32 mg/l, hydrogen carbonate 74 mg/l, magnesium 8 mg/l, sulphate 9 mg/l. The pH-value is 7. For each single lid 5 mL Volvic water was used as nutrient solution added with one globule of one of the substances during the pre-test phase. The results of all pre-tests were evaluated by ANOVA models. The most pronounced effects were observed for a treatment with sulphur LM VI compared to phosphorus and natrium muriaticum as well as compared to 200c.

Preparation of constant laboratory conditions

In accordance with recommendations of the International Seed Testing Association (ISTA), germination tests were run in a room meeting exact requirements regarding temperature and light control in order to make accurate and reproducible conditions. Temperatures were carefully checked throughout the room at the level of the substrate to be sure that temperature does not deviate from the by more than 1°C, since poor air circulation and hot spots from lights or light ballasts are the most common causes of temperatures that are too high or too low. The temperature at which the germination room is set depends on the species being tested.[20] To achieve constant laboratory conditions, temperature was kept at 20°C ± 1°C as monitored and recorded by a thermometer/hygrometer (Hygrometer testo 608-H1; Testo AG, Lenzkirch, Germany). Similarly, humidity in the laboratory was kept at 50% ± 10% (Hygrometer testo 608-H1). Immediately after finalizing the treatment of the grains, the laboratory room was kept dark for the experiment lasting for seven days. Seven days were chosen according to the recommendation of ISTA.[21]

Four experiments – four subsequent weeks

During the planning phase of the test series, it was projected to have five experiments in total. The first experiment was considered as test phase of the theoretical consideration for the practical handling under real world conditions. After having successfully completed this test procedure, the next four tests were conducted within 4 weeks. The results of the four experiments then formed the basis for statistical evaluation. On day one of each experiment (Sundays, beginning 9.00 a.m.), the wheat was treated and the jars were wrapped within 3 h, remained for 7 days in darkness followed by harvesting on day seven (Saturdays, beginning 9.00 a.m.), which took equal 3 h to complete. On Saturdays afternoon the next jars were prepared for the start of the consecutive experiment on the following day.

Cleaning of jars

The jars were cleaned in a dishwasher followed by a second washing process in the same dishwasher. After having finalized it, the jars were washed with double distilled water and sterilized by 180°C for 30 min. This procedure was executed prior to each experiment.

Selection of seed

The seed cultivar 'Florida' was harvested in 2007 and pre-selected by IPK Leibniz utilizing a sieve seize of 2.8 mm. The grains were scrutinized again before used in the experiment to ensure grains of the same size and kind. This procedure was executed prior to each experiment.

Preparation of wheat

The grains were pre-treated one day prior to the experiment with 60% ethanol and double distilled water as described below. Common agricultural seed dressing uses herbicides and pesticides to minimize seed diseases.[22] Wheat experiments would be significantly affected by using herbicides and pesticides. Therefore, we performed seed dressing by applying two times 0.13 mL of 60% ethanol to the grains on a plate covered with an absorbent

paper per puff followed by spraying double-distilled water with two puffs (0.13 mL each) one day prior to the start of the experiment. The grains were then applied to another plate with an absorbent paper enabling them to dry for 12 h. In this way, disinfected seeds were obtained for the subsequent experiment. This short term exposition of very small amounts of ethanol exhibits no toxic effects.[23]

Method

Experiment: start (day 1):

Placement of grains: The grains were placed on the upside down placed glass lid of a glass jar (diameter 11 cm) which was covered with a piece of the filter paper. The grains were positioned with the grain furrow facing downward (Figure 2).

Labels A, B, C for sulphur, placebo, water: Prior to a single experiment, two vials (for sulphur LM VI and placebo) were filled with globules by a person not involved into the experiment; a bottle of Volvic water (referred to hereinafter simply as 'water') was prepared as nutrient solution. A person not involved in the experiment assigned labels A, B, and C to the three treatment groups sulphur LM VI, placebo, or water. While the vials containing sulphur LM VI and placebo globules were blinded by the respective labels, water could not be blinded for obvious reasons. The assistant kept the label information and released it to the statistician (AG) in the meta-group 'central' and to the experimenter (KT) in the meta-group '*in situ*' at the end of the experiment week. Before starting the meta-randomization ('central' vs. '*in situ*'), the filter was placed on each lid and 20 grains were placed on the paper. All lids were then placed on a table in the laboratory with 10 columns, each containing 6 lids in a vertical line (Figure 3). The columns were assigned alternately for 'central' and '*in situ*', thus avoiding location effects.

***Meta-randomization* 'in situ' *versus* 'central'**: Lids were assigned one after the other to mimic the sequence of patients entering a doctor's office or ward. The meta-randomization between '*in situ*' and 'central' was based on a randomization list which was prepared by the statistician (AG). This randomization list determined whether the next lid is one from an '*in situ*' or a 'central' column and further processed according to '*in situ*' or 'central' randomization/unblinding.

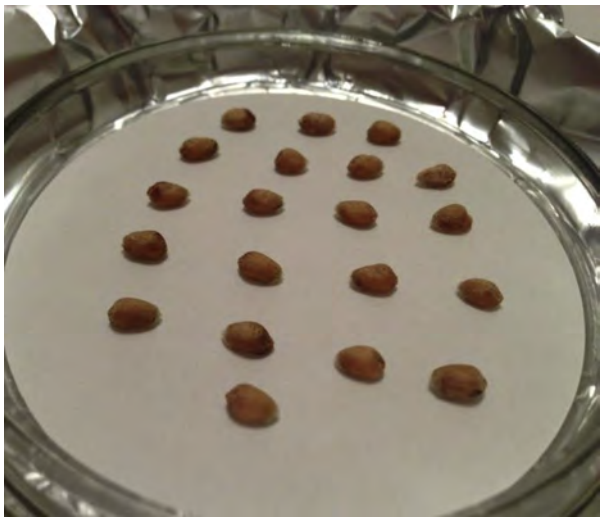

Figure 2 Pre-selected grains were placed on the upside down placed glass lid of a glass jar.

Figure 3 Arrangement of lids on the table.

Randomization* 'in situ' *(Figure 4): For the randomization '*in situ*', five envelopes were prepared by the experimenter, one for each '*in situ*' column. Each envelope contained six cards (two with label A, two with B, and two with C). As every column has 6 lines, an equal distribution of all three groups was ensured (block randomization).

One card out of the envelope was drawn by the experimenter (KT) without replacement to determine the substance which was added to the current lid in the '*in situ*'-group that was next according to the randomization list. Independent of the assigned substance (sulphur LM VI, placebo or water only) each lid was first pipetted with 5 mL of water prior to each treatment. Following randomization, the current lid received treatment A, B, or C: in case of homeopathic substance (sulphur LM VI) or placebo one globule was added blindly, while the water lids did not receive additional treatment.

After each single treatment the respective lid was immediately covered with a glass jar and wrapped in an aluminium bag (Figure 5a and b). The aluminium bag was then tagged with a code consisting only of column and line number (Figure 5b) thereby allowing no inference on type of randomization or treatment. Treatment and bagging of each lid lasted approximately three minutes.

At the end of the total sowing procedure (day 1 of the experiment), the completed randomization list with the group labels (A, B, and C) of the '*in situ*' randomization was kept under lock and key by the assistant not involved in the experiment.

Randomization 'central': A randomization list for the 'central' randomization was provided by the statistician (AG) before the start of the experiment. The randomly allocated treatment A, B or C was applied in the same manner as for '*in situ*' lids. Each lid was then covered with a glass jar and wrapped with an aluminium bag immediately after treatment. The aluminium bag was then tagged with a code consisting only of column and line number thereby

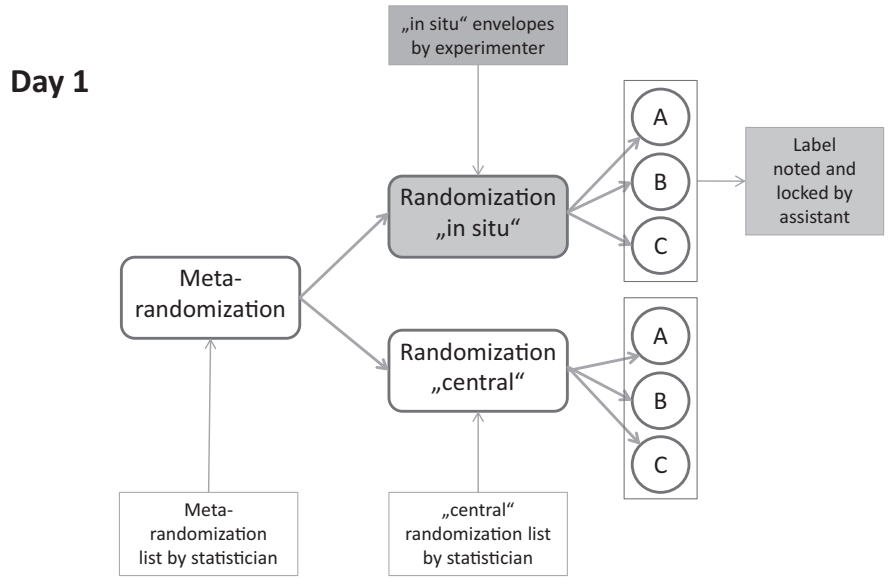

Figure 4 Meta-randomization and randomization procedures on day 1 (grey box: at laboratory, white box: outside laboratory).

allowing no inference on type of randomization or treatment. Treatment and bagging of each lid lasted approximately three minutes.

Experiment: end (day 7):

Harvesting: The grains of the lids were harvested after 7 days in the same sequence as originally pipetted. Germination and growth length was measured according to ISTA.[15] Measurements were then categorized as follows: non-germinated (NG), germinated with <1 mm (G < 1) und germinated with ≥1 mm (G ≥ 1). Germination is defined when the radicle has broken through the seed coat.[17]

Growth of grains includes up to five roots and a single stalk (coleoptile). In order to assess germination in our experiment, either root in the absence of stalks or − if grown − stalks were measured. The roots were measured connected to the grain, while the stalks were separated at the so-called 'weak point' of the grain for individual measuring (Figure 6a and b) following the recommendation of ISTA. Measuring was carried out by placing the coleoptile e.g. on a millimetre paper with a grid spectrum of 1 mm per square. Only germinated grains were measured. Abnormal seedlings, NG and dead seedlings were assigned to category NG. Figure 7 summarizes the procedures on day 7. Grains placed in each single lid were measured within three minutes. This time interval is equal to the treatment procedure thereby guaranteeing equal time slots between measurement and treatment.

Data entry for* 'in situ' *group: After having measured all grains of one lid in the '*in situ*' group, the document with the results of the 20 grain measurements was immediately submitted to the statistician via e-mail to avoid changes in the data after unblinding. After submitting the data of one lid, its code was unblinded to the experimenter by another person according to Beauvais proposal of '*in situ* unblinding'.

Data entry for the 'central' group: The grains of each lid of the 'central' group were measured and the results entered into a data list. In contrast to the '*in situ*' group, the labels of the 'central' group were not communicated to the experimenter.

Statistical analysis

Measurement data are categorized into NG seeds, seeds germinated with <1 mm (G < 1) and with ≥1 mm (G ≥ 1). Measurements below 1 mm cannot be further differentiated such that the length measurements are left censored at the detection limit of 1 mm. Furthermore, the distribution of the measurements above 1 mm showed a clearly non-normal distribution (Suppl. Figure 1) that could not be transformed to normal either (e.g., by log-transformation) even when taking the left-censoring into account. From a biological point of view a distinction between NG, germinated but not yet grown and grown seeds was regarded as capturing the most relevant aspects of the outcome.

Categorized measurements are presented as counts and percentages. Logistic regression models are used to compare various groups with respect to this categorized outcome. These models include a random effect with compound symmetry structure to allow for correlation between seeds in the same lid. Fixed effects are week (1−4), meta-randomization group ('*in situ*' vs. 'central'), treatment group (sulphur, placebo or water), and the interaction of meta-group with treatment group. The test for this interaction term directly corresponds to a test of Beauvais' hypothesis and was thus pre-selected to be the primary statistical test.

Since the proportional odds assumption was clearly rejected, odds ratios (together with 95% confidence intervals) are given separately for the two dichotomous sub-models NG vs. (G < 1 & G ≥ 1) and G ≥ 1 vs. (NG & G < 1) which correspond to effects on germination and on growth above 1 mm, respectively (since the three-stage outcome is ordinal, a comparison of G < 1 vs. (NG & G ≥ 1) is not given). P-values of the interaction of meta-group with treatment group are given for each sub-

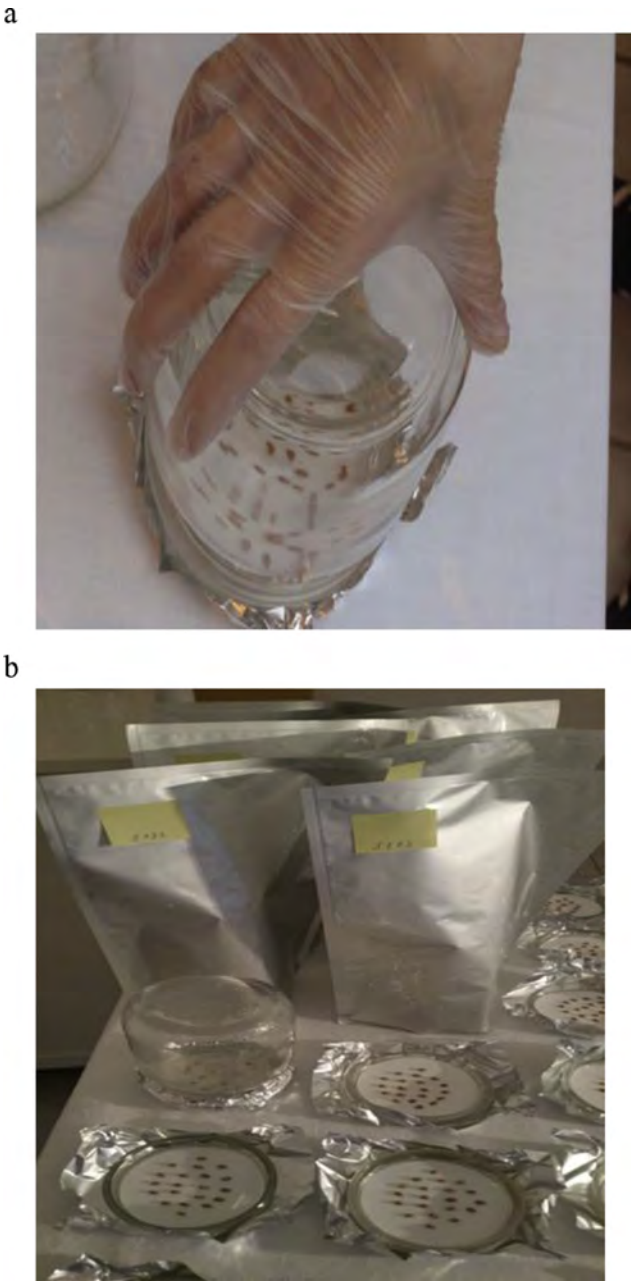

Figure 5 a: Covering of a glass lid with a glass jar. b: Wrapping in aluminium bags and tagging with a code.

model. Note, however, that the primary test for the interaction mentioned above refers to the full model using the outcome with three categories.

Two-sided p-values ≤0.05 were regarded as statistically significant. All statistical analyses were done using SAS 9.4 (SAS Institute Inc., 2012).

Results

The percentage of NG seeds, seeds germinated with <1 mm (G < 1) and with ≥1 mm (G ≥ 1) are shown for each week in Figure 8. While there are some treatment effects with respect to germination and length below 1 mm, (NG vs. G < 1 vs. G > 1) as described above, hardly any effect can be seen among those seeds that exhibit a length of at least 1 mm (Figure 8). If calculated across weeks in the '*in situ*' meta-group there were 9.6% NG, 36.9% G < 1 and 53.5% G ≥ 1 under sulphur treatment and 14.7% NG, 30.9% G < 1 and 54.4% G ≥ 1 under placebo treatment. With 'central' randomization/unblinding we observed 14.4% NG, 28.9% G < 1 and 56.7% G ≥ 1 under sulphur treatment and 14.3% NG, 33.5% G < 1 and 52.2% G ≥ 1 under placebo.

The effect of sulphur vs. placebo relating to all three stages (NG vs. G < 1 vs. G ≥ 1) is significantly different between '*in situ*' group and 'central' group (p = 0.003 for the interaction test). This is the p-value corresponding to our primary research question and is a finding clearly in favour of Beauvais' hypothesis. The results of the logistic regression models of the two dichotomous sub-outcomes (NG vs. (G < 1 & G ≥ 1); G ≥ 1 vs. (NG & G < 1)) are summarized in Table 1. Odds ratios of these models quantify the pairwise treatment group comparisons within each meta-randomization group.

Under '*in situ*' randomization/unblinding the odds of a seed not to germinate is 40% lower if treated with sulphur compared to placebo (OR = 0.60, CI 0.42−0.85, p = 0.004). In contrast, these odds are practically equal in the 'central' meta-group (OR = 1.01, CI 0.73−1.40, p = 0.954). However, this difference between the '*in situ*' and the 'central' meta-randomization group regarding the effect of sulphur vs. placebo relating to NG (vs. (G < 1 & G ≥ 1)) is not statistically significant (p = 0.061 for the interaction test).

Under '*in situ*' randomization/unblinding the odds of a seed to germinate with a length ≥1 mm are practically equal if treated with sulphur or with placebo (OR = 0.96, CI 0.79−1.17, p = 0.717). Moreover, these odds are 21% higher under sulphur compared to placebo in the 'central' meta-group, albeit not statistically significant (OR = 1.21, CI 0.99−1.47, p = 0.062). Again, the difference between '*in situ*' group and 'central' meta-group regarding the effect of sulphur vs. placebo relating to G ≥ 1 vs. (NG & G < 1) is not statistically significant (p = 0.161 for the interaction test).

The odds ratios for the comparison between placebo and water are very close to one (with correspondingly high p-values) demonstrating the legitimacy of the placebo.

Discussion

When Beauvais introduced the idea of a new type of randomization/unblinding, which he called '*in situ*', he hypothesized that randomized studies based on this type of randomization/unblinding lead to more pronounced effects in placebo controlled randomized homeopathy trials.[2] His paper was first published in the Homeopathy. Thereupon, Peter Fisher invited the homeopathic community to verify Beauvais' theory in practical experimental methods whereby the involvement of nonlocal mechanisms in homeopathic treatment might be tested.[9]

We accepted the challenge and started with the implementation. For our present study we chose the setting of homeopathic basic research using plants to investigate

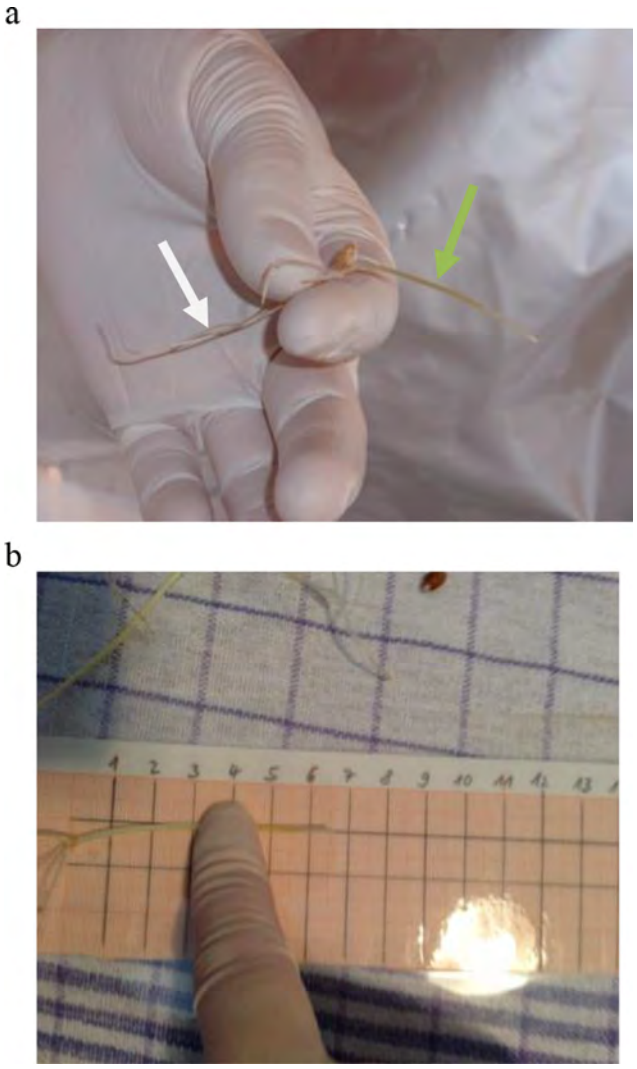

Figure 6 a: Stalk grown from the grain (White arrow: root/s; green arrow: coleoptile/single stalk). b: Measurement of stalk length by help of a millimetre paper. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Beauvais' idea. The testable prediction was that the difference between placebo and homeopathic substance vanishes in trials using a common central randomization and unblinding procedure due to 'smearing' (i.e. specific effects occurring in the placebo group), while 'smearing' is avoided by *in situ* randomization/unblinding.

In the following, we focus on sulphur LM VI and placebo. The three-stage length distribution under sulphur was significantly different between the meta-groups ('*in situ*' vs. 'central'; $p = 0.001$). Considering the results for placebo in both meta-groups ('*in situ*' and 'central'), there was no significant difference ($p = 0.481$) in contrast to what might be expected from Beauvais' suggestion. The main result of the experiments revealed that the difference between sulphur and placebo group relating to all three stages (not germinated, germinated with <1 mm, and germinated at least 1 mm) is significantly different between '*in situ*' and 'central' meta-group ($p = 0.003$).

When comparing week 1 with weeks 2–4 in Figure 8, it is obvious that the results in all groups and meta-groups are markedly different. Therefore, in a further statistical analysis, we investigated a potential interaction between week (1–4) and the important effect modification of treatment group by meta-randomization group (Beauvais' hypothesis). This revealed indeed a statistically significant difference between week 1 vs. weeks 2–4 with respect to Beauvais' hypothesis: while there is no statistically significant difference between '*in situ*' and 'central' with respect to the sulphur effect in week 1 ($p = 0.517$) the results for weeks 2–4 ($p < 0.001$) were quite similar to those for all weeks 1–4. One conjecture regarding this time effect is that in week 1 the experimenter (KT) was completely focussed on the comprehensive and correct implementation of the experimental design. In the following weeks, the focus has been more directed back to grains and substances based on years of routine in handling.

If entanglement between experimenter, substances and grains is occurs, as hypothesised by Milgrom, Walach,

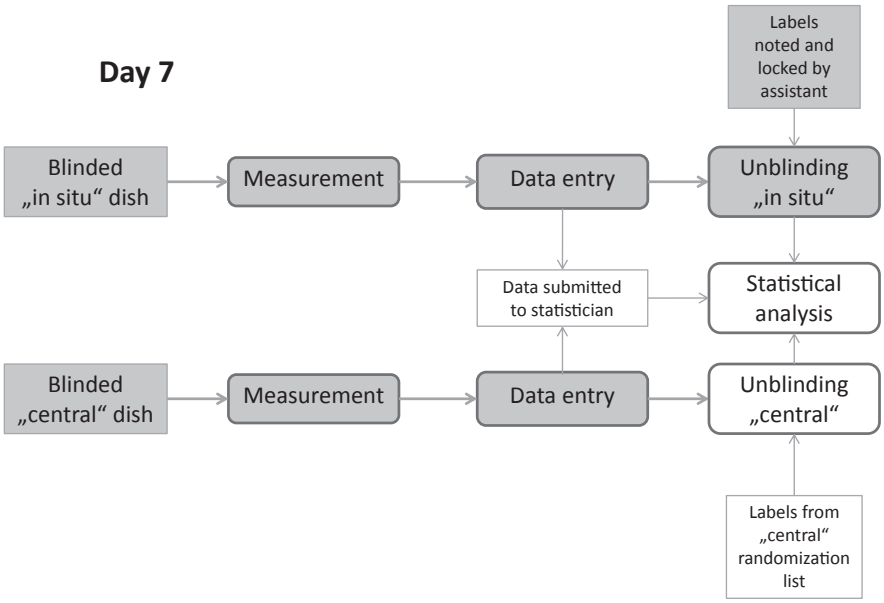

Figure 7 Measurement and data collection procedure at day 7 (grey box: at laboratory, white box: outside laboratory).

Table 1 Odds ratios (OR) with 95% confidence interval limits (CI) and p-values (p) for both dichotomous submodels (NG vs. (G < 1 & G ≥ 1); G ≥ 1 vs. (NG & G < 1)), both meta-randomization groups (meta) and all pairwise comparisons between treatment groups (bold letters: primary comparison between sulphur and placebo group)

Outcome	*Meta*	*Group 1 vs.*	*Group 2*	*OR*	*95% CI*		*p*
NG vs. (G < 1 & G ≥ 1)	*In situ*	**Sulphur LM VI**	**Placebo**	**0.60**	**0.42**	**0.85**	**0.004***
		Sulphur LM VI	Water	0.57	0.40	0.81	0.001*
		Placebo	Water	0.95	0.69	1.31	0.768
	Central	**Sulphur LM VI**	**Placebo**	**1.01**	**0.73**	**1.40**	**0.954**
		Sulphur LM VI	Water	0.92	0.67	1.27	0.620
		Placebo	Water	0.91	0.66	1.26	0.579
G ≥ 1 vs. (NG & G < 1)	*In situ*	**Sulphur LM VI**	**Placebo**	**0.96**	**0.79**	**1.17**	**0.717**
		Sulphur LM VI	Water	0.93	0.76	1.13	0.467
		Placebo	Water	0.96	0.79	1.17	0.716
	Central	**Sulphur LM VI**	**Placebo**	**1.21**	**0.99**	**1.47**	**0.062**
		Sulphur LM VI	Water	1.19	0.98	1.45	0.087
		Placebo	Water	0.98	0.81	1.20	0.878

* Significant after correcting for multiple testing (in two submodels and two meta-randomization groups each).

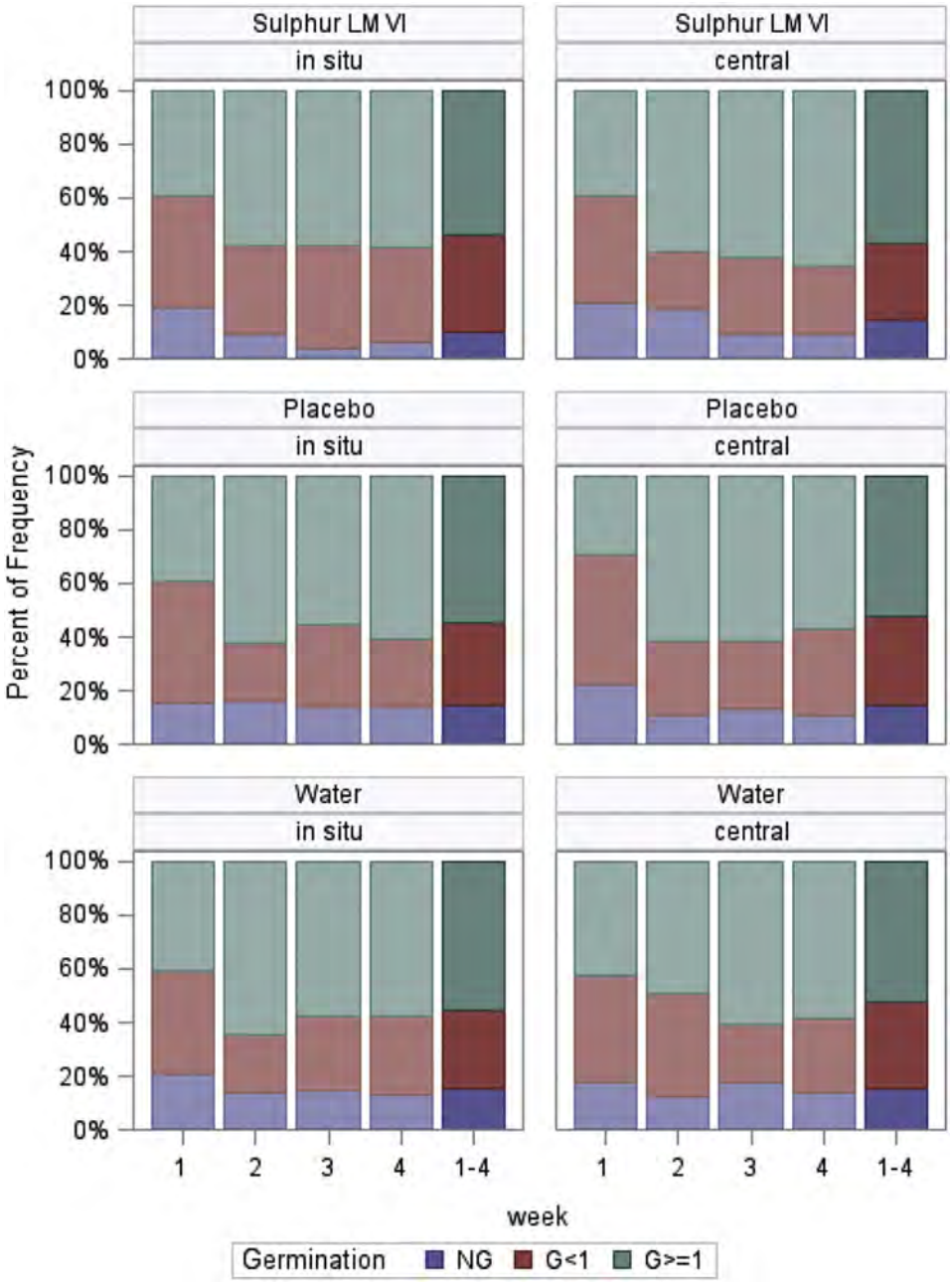

Figure 8 Percent of non-germinated (NG), germinated with <1 mm (G < 1), and germinated with ≥1 mm (G ≥ 1) by meta-randomization group (*in situ* vs. central), treatment group (sulphur LM VI, placebo, water) and week (1−4 and total '1−4').

Beauvais, Almirantis, and others, it might be possible to experimentally observe the effects of such interaction between experimenter (KT), substances and grains. A first step in the setting of a plant model has now been made. Beside independent repetitions of our experiments, it is up to clinical trials to substantiate Beauvais' hypothesis. The proposed design can be performed without much additional time and effort and may be employed within the next homeopathic study.

The real test of this kind of models is not whether they explain previously known features of homeopathy, but whether they can be used to improve the design of experimental and clinical tests of homeopathy's core hypothesis that high dilutions are different from appropriately prepared placebos.[24]

To summarize we found a statistically significant overall difference with regard to a sulphur effect between the two meta-randomization groups, thus corroborating Beauvais' hypothesis. This difference is mainly due to a pronounced germination of sulphur compared to placebo under '*in situ*' randomization/unblinding and, to a minor degree, to a sulphur growth effect (germination with $\geq$1 mm) under 'central' randomization/unblinding. This last result, although not statistically significant, seems to be not in line with Beauvais' suggestion who predicted weaker effects under central randomization. However, this is in part again counterbalanced by the length measurements $\geq$ 1 mm which do not show considerable differences between groups nor between *in situ* and central randomization (Suppl. Figure 1).

Conflict of interest

The authors declared no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.homp.2016.05.002.

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