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From Basic to Applied Science: The Case of the Differential Outcomes Procedure

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Abstract

A major health and societal challenge nowadays is how to ameliorate and/or delay the onset of cognitive decline in humans suffering from diverse pathologies. Often, solutions can be found in basic science conducted in the laboratory through the use of very well-known experimental procedures. In the present review article, we set out to present the main findings from a research line focused on an experimental procedure originally discovered in animal studies investigating associative learning; namely, the differential outcomes procedure (DOP). Here we review the main findings of the DOP that relate to the different processes involved in associative learning and memory from a neuropsychological perspective. We take a step forward to illustrate how the DOP can be applied to real life settings to address important issues such as treatment adherence. Briefly, we first show how the DOP can be adapted to enhance discriminative learning and memory retention in children of different ages, younger adults, and healthy as well as pathological aging. Next, we illustrate how the DOP can be a cost-effective approach to tackle health challenges such as adherence to medical prescriptions in older people suffering from multiple morbidities. Finally, we discuss digital, mobile-based applications using the DOP to promote autonomy in older adults. Future directions in the DOP applications to health issues are also presented.

Keywords: Basic science, applied science, associative learning, memory deficits, differential outcomes procedure.

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Acronyms

AD: Alzheimer's disease

DOE: Differential outcomes effect

DOP: Differential outcomes procedure

MCI: Mild cognitive impairment

NOP: Non-differential outcomes procedure

R-O: Response-outcome association

S-O: Stimulus-outcome association

S-R: Stimulus-response association

SEPEX: Sociedad Española de Psicología Experimental (Spanish Society of Experimental Psychology)
WHO: World Health Organization

Introduction

One of the current challenges of science is how to continue to generate new knowledge through basic research that can be readily applied to real life problems. Although notable efforts have been recently made, findings from psychological research in the laboratory are often communicated only to the scientific community and not translated to clinical practice (e.g., Werner-Seidler et al., 2016). The segregation between non-human and human research is also striking. While research on associative learning has been predominantly conducted with animals, research on higher-order cognitive functions such as perception, attention, memory or language has mostly involved human participants. Twenty-five years ago, the Spanish Society of Experimental Psychology (SEPEX) was born with the mission to promote the integration of experimental studies from traditionally segregated fields of psychological science, as well as to lay the foundations for translational science. While the former has been largely and successfully achieved, the latter remains a goal for the future. The case of the differential outcomes procedure can be considered paradigmatic in this regard (Mateos & Flores, 2016).

In this review article, we aim to illustrate how the *differential outcomes procedure* (hereafter the DOP), which was imported from animal studies in the field of associative learning, has evolved to address important questions related to discriminative learning and memory in healthy humans and in clinical populations. Specifically, we propose that this easy-to-implement procedure has the great potential to be used in medical settings to promote autonomy in older adults with respect to adherence to medical treatments.

In the following sections, we address the aforementioned learning procedure, its principles and mechanisms from an interdisciplinary approach. We then illustrate its effects on discriminative learning and memory in different populations, from childhood to the elderly, with or without pathologies. Finally, we present recent data in which we have adapted the procedure for use in medical settings.

The differential outcomes procedure: Principles and mechanisms

Neutral signals can acquire, through classical conditioning, behavior-controlling properties that favor the survival of organisms. A good example of how a neutral stimulus acquires significance is found in Ivan Pavlov's early experiments. Hungry dogs salivated (the conditional response) when a particular *neutral* stimulus, such as a lighted circle (the conditioned stimulus), appeared repeatedly only before the food supply (the reinforcer), but not when a different neutral stimulus (e.g., a lighted square) was presented without being followed by any reinforcer (reported in Pavlov, 1927). However, more relevant to the DOP-based research is the phenomenon of operant conditioning, where appropriate actions lead to rewarding consequences, as it is observed in Thorndike's (1911) earlier experiments. Hungry cats learned to escape from puzzle boxes by doing a number of actions such as pressing levers and were rewarded with food when they successfully completed the escape responses. This example of discriminative learning, involving operant conditioning with animals, is also essential for humans. For instance, people learn to cross the road only when the traffic light turns green, and to stop when it turns red; or to take the umbrella when the sky turns gray, and the sunglasses when the sun comes out. Thus, discriminative learning is essential for all organisms to adapt to their environment.

First demonstrations in animals and humans

In the laboratory, discriminative learning has largely been studied in animals, and Trapold (1970) was the first to demonstrate that this learning could be enhanced by the way in which reinforcers were delivered. In Trapold's experiment, rats were presented with two choices in a Skinner box, so that they had to learn to press one lever (e.g., the lever on the right) when a tone sounded, and to press the other lever (e.g., the lever on the left) when a click sounded. To promote learning, subjects were reinforced with sucrose (sweet water) or pellets (food) after each correct response. In the standard common-outcome condition, when subject's responses were correct, the same reinforcer (e.g., pellets) followed each stimulus-response association. However, Trapold observed that learning acquisition was accelerated and enhanced (higher final accuracy) when each stimulus-response association was followed by a unique reinforcer. For example, pressing the right-hand lever (Response 1) in the presence of a tone (Stimulus 1) resulted in the reinforcer sucrose (Outcome 1), whereas pressing the left-hand lever (Response 2) in the presence of a click (Stimulus 2) resulted in the reinforcer pellet (Outcome 2). Thus, a differential outcome effect (hereafter, DOE), characterized by faster and more accurate learning, is typically found in conditional discriminative learning situations in which each response is followed by a unique and specific outcome (DOP; Trapold, 1970; Trapold & Overmier, 1972). The advantage of using the DOP, compared to the *non-differential outcomes procedure* (hereafter the NOP) where the outcomes are randomly presented, or the *common-outcome procedure* where a single outcome is provided, has been observed in different species (rats, dogs, pigeons) and with various reinforcers (reinforcers that differ in quality or quantity; Goeters et al., 1992; Urcuioli, 2005). For the sake of clarity, we will henceforth refer to the different phases of discriminative learning with the following terminology: cues (e.g., tone, click) will be referred to as *sample* stimuli; choices (e.g., lever on the right, lever on the left) will be referred to as *comparison* stimuli, and the reinforcers (e.g., sucrose, pellets) will be referred to as *outcomes*. Figure 1 illustrates the three different phases of the DOP and NOP.

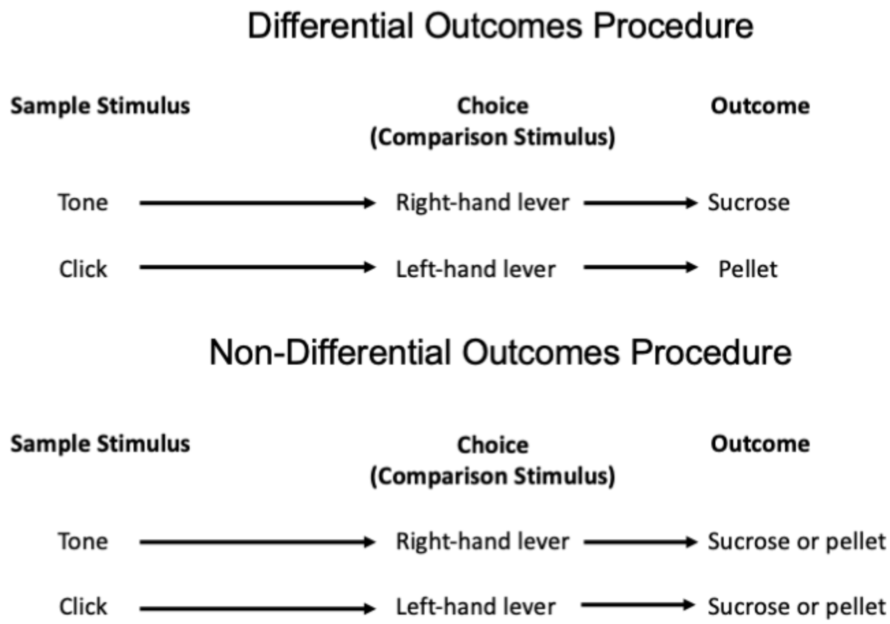

Figure 1. The three phases involved in conditional discriminative learning under the DOP and the NOP. In tasks such as the matching-to-sample task, subjects are told to select which stimulus of the different alternatives (choices) matches the previously presented sample stimulus. In that kind of tasks, we usually refer to the choices as comparison stimuli (Adapted from Trapold's experiments).

In humans, early demonstrations of the advantages of the DOP in conditional discriminative learning were restricted almost exclusively to young children (Estévez et al., 2001; Estévez & Fuentes, 2003; Maki et al., 1995), persons with mental disabilities (Litt & Schreibman, 1981; Malanga & Poling, 1992; Saunders & Sailor, 1979; Shepp, 1962) or neurological patients (Joseph et al., 1997). Researchers suggested that the DOP advantage would be observed only in those individuals who, given their young age or mental state, would not be able to use sophisticated learning strategies such as verbal rules. For instance, Estévez et al. (2001) used a matching-to-sample task involving symbolic stimuli in children aged 4.6 to 8.6 years. The children had to match two comparison stimuli with their corresponding sample stimuli, and correct choices were followed by two types of outcomes, toys or candies. The authors observed a significant DOE in children under the age of 6 years (see also Maki et al., 1995), but the DOP did not yield significant effects in children aged 7.6 and 8.6 years. However, in a second experiment with the older children group, they observed a significant DOE when the number of comparison stimuli that had to be paired with the two sample stimuli increased from two to four, making the task more difficult. Estévez et al. (2001) suggested that for the DOP to have an effect on performance, the task has to be sufficiently challenging for the participants. Therefore, task difficulty seems to be an important factor to take into account when implementing the DOP in different populations.

Mechanisms underlying the differential outcomes effect

So far, we have described the DOP and found it to be a suitable procedure for enhancing conditional discriminative learning in both animals and humans. Why does arranging the outcomes differentially enhance learning? One answer to this question comes from the so-called two-process learning theories (Trapold & Overmier, 1972; for a review, see Overmier et al., 1999). Based on Thorndike's *law of effect*, when a specific response is given to a specific stimulus, and that response is immediately rewarded with a reinforcer, a specific stimulus-response association is learned. Importantly, the reinforcer would act as a mere qualifier (catalyst) of that association, but it is not part of the learned association. Based on this, learning should not be affected at all by the use of different reinforcers. On the other hand, the two-process theory suggests that the reinforcement process gives rise to two associations: one involving the stimulus and the response (S-R) and one involving the stimulus and the reinforcer (outcome) (S-O). Therefore, both associations are relevant in the discriminative learning process. Initially, it was suggested that pairing a stimulus with a reinforcer endowed such stimulus with general motivational properties (e.g., Rescorla & Solomon, 1967) that would produce enhanced learning. However, the results of subsequent studies showed that the DOE cannot be solely explained as a result of general motivational effects (see Urcuioli, 2005, for a review). Accordingly, Trapold and Overmier (1972) theorized that when a specific S-R association is followed by a unique outcome, subjects learn something about the qualitative and quantitative properties of the outcome, creating an *expectancy* of which outcome will appear. Such an expectancy is conditioned by classical conditioning (*conditioned expectancy*) and has stimulus-like properties which guide the choice of the appropriate response. On the basis of this theory, outcomes expectancies not only motivate the organisms but also provide them with a source of information that can complement or serve as an alternative to the information provided by the discriminative stimulus (Overmier & Lawry, 1979). It is rather recently that we have learned that such expectancies, or the representations (prospective memories) of the specific outcomes, can be activated implicitly and unconsciously, *i.e*. without intention (Martínez-Pérez et al., 2021) and even without participants being aware of presence of the sample stimuli or the outcomes through the use of masking conditions (Carmona et al., 2019a). Here it is important to note that the advantage of creating a conditioned expectancy will occur only when prospective memory representation of a unique outcome is activated, as is the case in the DOP. When outcomes are randomly presented after each S-R association, such a conditioned expectancy would involve memory representations of the different outcomes and therefore expectancies would not help guide response selection. In such cases, the choice must rely on retrospective memory of which response was associated with which sample stimulus. Figure 2 illustrates the conditioned expectancy theory in the differential and non-differential learning conditions.

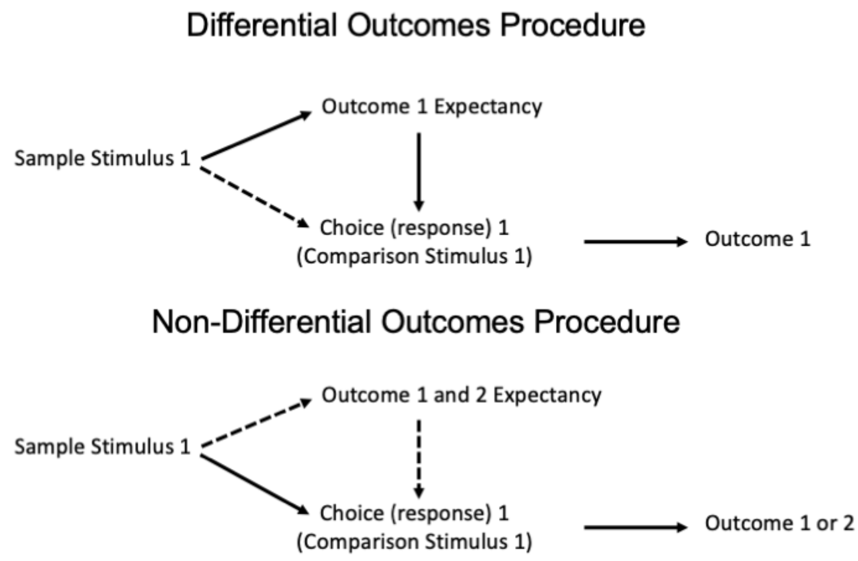

Figure 2. The conditioned expectancy theory suggests that, in the DOP, the repeated use of a unique outcome after each S-R association creates a conditioned expectancy of the forthcoming unique outcome. This expectancy would act as a conditioned stimulus by classical conditioning that guides the selection of the appropriate response (solid lines). With the NOP, the conditioned expectancy is also created, but it refers to both outcomes and therefore does not provide additional information to guide response selection (dotted lines).

According to the conditioned expectancy theory, the DOP activates a form of prospective memory that guides the selection of the correct response (or comparison stimulus), whereas the NOP relies only on a form of retrospective memory about which response (or comparison stimulus) goes with a particular sample stimulus. Importantly, this statement has some relevant implications for both basic and applied psychology. Research with the DOP may be useful for exploring the role of specific neural systems involving both prospective and retrospective memory types in conditional discriminative learning. The two-memory systems theory, an evolution of the conditioned expectancy theory, argues that different neuroanatomical circuits are involved in the DOP and NOP. Thus, learning performance under the DOP would depend on the integrity of a glutamatergic-dependent memory system involving activation of the basolateral amygdala in the developmental phase, and the orbitofrontal cortex in the maintenance phase, and typically occurs when hedonic reinforcers are used in animal studies (e.g., sweet water, food) (Savage et al., 2004; Savage & Ramos, 2009). In humans, the DOP would activate two types of brain areas, those that correspond to the perceptual content of the outcomes (e.g., modality-specific visual or auditory cortices) and those involved in modality-independent prospective memory, such as the posterior lateral parietal and dorsolateral prefrontal cortices (Mok, 2012; Mok et al., 2009). In contrast, learning performance under the NOP has to rely on a cholinergic retrospective memory system that depends on both delay and working memory capacity, in which the hippocampus is involved. These two neuroanatomical networks have been corroborated by lesions studies in animals. Lesions of the basolateral nucleus of the amygdala alter the performance of rats under the DOP, but not under the NOP (Savage et al., 2007). In contrast, hippocampal lesions affect the performance of rats under the NOP, but not under the DOP (Savage et al., 2004).

Although the conditioned expectancy theory has received the most support in the field of the DOP, other alternative explanations have been put forward. For instance, several authors have proposed that during discriminative learning, in addition to S-O associations, participants can also learn associations between each response and its corresponding outcome (R-O), which could guide goal-directed behavior as well (Wit & Dickinson, 2009). Accordingly, Estévez et al. (2003) conducted a series of experiments in which they examined the role of unique S-O and R-O associations in the DOE. The results of the experiments showed that when a unique association was established between the sample stimuli and the outcomes (S-O associations) or between the responses and the outcomes (R-O associations) there was an advantage in discriminative learning in the DOP conditions compared to the NOP conditions. The authors concluded that unique R-O associations may also contribute to the DOP advantage in conditional learning (see Urcuioli, 2005, for a review).

Regardless of its theoretical underpinnings, from an applied science point of view, the DOP may be a suitable tool that can be adapted to improve or ameliorate age-related memory deficits in healthy individuals, as well as in patients suffering from neurological pathologies. An important issue related to the potential applications of the DOP concerns its generalization effects, and one interesting procedure in that respect is *transfer of control* (ToC) (Maki et al., 1995; Rittmo et al., 2020). In the DOP, participants are able to establish stimulus-(outcome)-expectation associations, and expectation-response associations, and therefore in the ToC procedure, during the transfer phase they are able to infer the correct response in spite of never having previously been presented with these particular stimulus-response pairs. The contingency effects observed when adapting the standard DOP to a ToC setting have been explained in relation to the concept of *stimulus class formation* (Lowe, 2020; Urcuioli, 2013). That is, multiple stimuli can be grouped together in relation to their association with a specific outcome-expectation, and through the association of the specific expectation with a particular response the participants can infer the correct response. Thus, this procedure may offer a way to generalize differential outcomes effects to non-trained stimuli. The applications of the DOP will be discussed in the following sections.

From animal to human studies

The strong evidence supporting the positive effects of the DOP regarding improvements in learning and memory in animals led the procedure to become the focus of a growing series of human experimental research. The benefits of using DOP have been demonstrated in different populations that often report difficulties in the processing of symbolic discriminations, such as children and adults with Down syndrome or children born prematurely. Estévez et al. (2003) conducted a study to explore whether the DOP could improve discriminative learning in children and adults with Down syndrome using a delayed-to-sample symbolic matching task. Participants received colored tokens (secondary reinforcers) following each correct response, that were presented differentially or randomly. After completion of the task, the tokens were exchanged for food or toys (primary reinforcers). The results showed that, regardless of their mental age, when children and adults with Down syndrome received differential outcomes after their correct responses, they were able to learn the task. However, when outcomes were randomly administered, they were not able to learn, and their performance remained about chance level.

Furthermore, Martínez et al. (2012) showed in their study with children born prematurely that the DOP can also produce improvements in visuospatial recognition. Specifically, they used a delayed visuospatial recognition task with two geometric figures as sample stimuli that could appear as comparison stimuli with a clockwise rotation of 90, 180 or 240 degrees. The study revealed that the visuospatial recognition of children born prematurely was significantly improved when differential outcomes were used. This suggests that the DOP could have great potential as an intervention tool in this specific population.

All of these studies rewarded participants using positive reinforcers after correct responses. But in everyday life, the consequences that follow our behavior may be diverse and involve, for example, the loss of something valuable when the response is not the expected or appropriate one. Some common situations could be the withdrawal of points from a driver’s license when committing a traffic offence or imprisonment if a crime is committed. To determine the impact of the types of consequences (positive reinforcement and response cost) on discriminative learning, Martínez et al. (2009) designed a delayed matching-to-sample task which was administered to 5-year-old children. In the DOP condition, participants received or lost a specific outcome following their correct or incorrect responses, respectively. In the NOP condition, they could also gain or lose a reinforcer, which in this case was randomized. The researchers implemented three types of training: i) the administration of a specific reinforcer after each correct response; ii) the withdrawal of a specific reinforcer after each incorrect response; and iii) the use of both procedures simultaneously. Regardless of the type of consequence used, associations trained with the DOP were better learned and remembered. After the training phase, participants completed three memory tests at 1 day, 1 week, and 1 month. The new results showed that the effects of the DOP on memory were long-lasting. Martínez et al. (2013) obtained similar results in 7-year-old children, supporting the efficacy of this procedure in the retention of learned information.

Subsequent studies showed that visuospatial memory of children aged 4 to 7 years can also be improved when each stimulus (everyday objects, abstract scenes, figures and locations) is associated with a specific outcome (Esteban et al., 2014, 2015). Findings from all these studies suggest that the DOP could have important implications in educational settings to enhance learning of complex subjects such as mathematics or language. This conclusion is further supported by a study done with young adults in the laboratory. Estévez et al. (2007) explored whether the beneficial effects of the DOP could help improve the discrimination of two mathematical symbols "<" and ">" (less than and greater than). To do so, they presented different versions of mathematical expressions to undergraduate students. The first trials of the task had no feedback and were used to determine whether participants had difficulty discriminating between the two symbols. This allowed the creation of two groups, one with difficulties to discriminate the symbols and another without difficulties. The results revealed that the group with difficulties showed increased accuracy and faster responses under the differential outcomes condition.

In addition to abstract stimuli, one type of stimulus frequently used in many of the experimental tasks conducted with adults has been photographs of human faces. Plaza et al. (2011) designed a set of delayed matching-to-sample tasks using human faces as stimuli and increased the level of difficulty in each experiment. According to previous studies with children, they found that, when the task was very simple, participants were able to solve it without the extra help provided by the DOP. When the task difficulty was medium, the DOE was only found with reaction times (participants were faster when they received differential outcomes after their correct responses compared to when random outcomes were used). They only found an advantage of the DOP over the NOP in response accuracy when the task was very challenging for the participants. The evidence so far supports that task-difficulty modulates the DOE magnitude. A recent meta-analysis of 43 experiments exploring the effectiveness of the DOP in humans found larger effect sizes in more difficult tasks (McCormack et al., 2019). Specifically, they observed larger effects on overall accuracy for symbolic and delayed matching-to-sample tasks relative to identity matching-to-sample tasks, and for transfer relative to overall and terminal accuracy. Similarly, animal studies suggest that the DOP advantage is more likely when stimulus control is more difficult to establish (e.g., when the stimuli are complex or difficult to discriminate; see Goeters et al., 1992, for a review). One explanation for the lack of DOEs with easier tasks could be ceiling effects. Although this explanation cannot be ruled out in some of the studies, the evidence so far suggests that the modulation of the DOE by task difficulty could also be explained in relation to the two-associative process theory. That is, in cognitively healthy adults and when the task is easier (e.g., learning two S-R associations only), the retrospective route to learning may be sufficient and efficient, and so the alternative expectancy route to learning may not add any further benefit. However, when the task is too difficult (e.g., learning many S-R associations), the retrospective route may not be sufficiently effective (e.g., when maintaining too much information in working memory is needed), and so learning will benefit from the alternative prospective expectancy route.

Available evidence seems to indicate that cognitive load could be an important factor in determining task difficulty. In fact, one of the strategies that researchers have employed to make the tasks more challenging is to increase the number of associations to be trained. Thus, to explore the amount of cognitive load necessary to elicit the beneficial effects of the DOP, Fuentes et al. (2020) conducted a study in which participants were required to learn three associations (low-load condition) or four associations (high-load condition) and compared performance in the DOP and NOP conditions. Long-term retention of such learned associations was assessed one hour and one week after the end of the training phase. Interestingly, participants were more accurate and had better long-term retention of the previously learned associations when the DOP was used, but only in the high-load condition. This finding suggests that the DOP is most useful when working memory is overloaded.

This hypothesis is further supported by sleep deprivation studies. It is well established that sleep loss, which is relatively common in our stressful lifestyle, can reduce vigilance or arousal levels affecting the performance of daily tasks. To explore whether the DOP could ameliorate the effects of sleep deprivation on memory, Martella et al. (2012) exposed a group of undergraduate students to controlled sleep deprivation in the laboratory. Subsequently, participants were required to perform a face recognition task similar to the one used in the study of Plaza et al. (2011). The results showed that the sleep-deprived group improved their performance under the differential condition, mainly for the short delay, when working memory was affected by low arousal. The results of this study showed that the DOP is useful in conditions in which the attentional capacity is affected and suggests its potential application in populations with problems derived from lack of sleep due to work requirements, lifestyle, age or even illness. A study conducted with other versions of this experiment, e.g., using faces with emotional expressions, also showed similar findings related to the difficulty of the task and, in addition, evidenced that, regardless of the emotional expression of the faces, those participants who received specific outcomes after their correct responses showed better face recognition than those who received random outcomes (Plaza et al., 2013). The recognition of people and their emotional expressions is an everyday activity that requires, to a large extent, the identification of face-specific features. In these cases, the DOP is presented as an identification aid (see González-Rodríguez et al., 2020).

Taken together, the results obtained in the aforementioned studies demonstrate that task difficulty may be a modulator of the effect of the DOP. They also point out that the beneficial effects of the DOP are mainly found in people who present learning or memory problems that make it difficult for them to use certain strategies. These characteristics give the procedure great potential for its implementation in intervention programs in populations with memory deficits, such as pathological aging.

The differential outcomes procedure in healthy and pathological aging

As it has been discussed in the previous sections, the beneficial effects observed in discriminative learning and memory with the use of differential outcomes can be best explained in terms of activation of a compensatory mechanism in the face of brain damage or/and cognitive impairment. Thus, we propose here that the DOP can be a novel, easy-to-implement, and cost-efficient approach to non-pharmacological interventions in healthy and pathological aging, and in other brain or psychiatric disorders. In the following two sub-sections we discuss the existing experimental evidence in older adults and in people with brain disorders, respectively, and the suitability of this approach for addressing cognitive and everyday functionality in these populations. We also highlight outstanding questions that need to be addressed in future research.

The differential outcomes procedure in healthy aging

Although aging is a highly heterogeneous process, we know that there are brain and cognitive changes associated with age, and that there is a relationship between cognitive functioning and the ability to cope with everyday activities (e.g., managing finances) and live independently (everyday functioning) (Hertzog et al., 2021; Martyr & Clare, 2012; Royall et al., 2007). In terms of cognitive changes, we know that memory is one of the main processes that declines with age, for instance a reduction in working memory capacity is associated with aging (Clapp & Gazzaley, 2012; McNab et al., 2015). Within this context, and in line with the processes and mechanisms proposed to underlie differential outcomes effects, we propose that the DOP can be an effective, and potentially scalable, approach to enhance cognitive and everyday functioning in healthy older adults.

Several studies support that the unique association of a particular outcome (e.g., pleasant pictures) to the to-be-remember stimuli has a boosting effect on memory performance. These studies have employed delayed matching-to-sample tasks, where participants are asked to remember a stimulus and after a delay, they have to select which of the comparison stimuli matches the previously presented one. López-Crespo et al. (2009) reported enhanced delayed recognition of faces, both with accuracy and speed measures, when unique differential outcomes were administered in a group of older adults; whereas in the group of younger adults the DOE was only observed for reaction times. Importantly, while the performance of older adults dropped drastically in the longest delay (30 seconds) when the outcomes were randomly administered (NOP), this was not the case for the differential outcomes condition. Actually, in that condition the performance of older adults did not significantly differ from that of the younger adults. A similar finding, memory performance not being affected by the delay manipulation in the DOP, was found for the group of younger adults but only with speed measures. Carmona et al. (2019b) extended these findings to delayed recognition of pictures of daily objects and showed an improvement in memory performance with differential outcomes training in a control group of nine older adults. Finally, Vivas et al. (2018) showed that the DOP was effective in enhancing visuospatial working memory in a group of cognitively healthy control older adults. That is, older adults showed significantly higher accuracy under differential outcomes (76%) relative to non-differential outcomes (65%) in a spatial delayed recognition memory task where they had to match the location of two squares to one of four prior locations presented sequentially. And this was the case regardless of the delay between the last location encoded and the match-to-sample response display (2 or 15 seconds). The finding in López-Crespo et al. (2009) of differential outcome effects being dependent on task difficulty (greater effect in longer delays, and only with speed measures in the younger adult group) is in agreement with some of the aforementioned studies by Estévez and collaborators (Estévez et al., 2001, 2007; Plaza et al., 2011). Overall, the findings across the studies with delayed matching-to-sample tasks converge to the idea that the DOP is a potent tool to enhance memory function in healthy older adults. These findings are also in agreement with those from animal studies which suggest that the DOP is effective in improving working memory in aged rats (Savage et al., 1999).

In conclusion, although few studies have been conducted so far with older adults, the findings are very promising for developing non-pharmacological intervention for enhancing cognitive function, and possibly delaying the onset (prevention) of cognitive impairment in older adults. In particular, the finding of improved visuospatial working memory with the DOP (Vivas et al., 2018) is important since spatial deficits (e.g., spatial disorientation) are recognized as an early sign of Alzheimer's disease, and could potentially be an early behavioral marker of the disease (Iachini et al., 2009; Salimi et al., 2018). Visuospatial abilities play also a fundamental role in everyday activities and support independent living; that is, they are crucial for many everyday activities such as wayfinding, geographical orientation, using a map of space for navigation, and reaching objects. Without diminishing the importance of these findings, further research is needed to better understand generalizability and transfer effects of memory benefits to non-trained tasks/stimuli and everyday life. This issue is highly pertinent given the little existing support for far transfer effects of more traditional cognitive training approaches (for a meta-analysis, see Sala et al., 2019).

The differential outcomes procedure in adult clinical populations

We have already argued that the DOP may be a potent tool to enhance learning and memory in healthy populations, who are not at the peak of their cognitive function and ability (e.g., children and older adults) or/and under particularly cognitively challenging tasks (e.g., mathematical associations in young adults). Experimental research evidence also supports the effectiveness of the DOP to address moderate and severe cognitive impairments in clinical populations with neurodegenerative brain disorders or other conditions.

In line with the findings from animal studies which support that the DOP can reverse lesion-induced working memory impairments (Savage & Langlais, 1995), Hochhalter et al. (2001) showed improved delayed recognition memory for faces in a group of four people with alcohol-induced dementia when differential outcomes were administered. In a later study with larger samples, Vivas et al. (2018) showed, using the visuospatial working memory task discussed above, that patients with mild cognitive impairment (MCI) and patients with Alzheimer's disease (AD) had significantly better performance in the DOP condition than in the NOP condition, regardless of the delay (2 or 15 seconds). The study also showed that AD patients needed more training to benefit from the differential outcomes manipulation and reached above-chance levels of performance only in the last trials. Two more studies conducted with AD patients have shown better delayed recognition for faces (Plaza et al., 2012) and pictures of everyday objects (Carmona et al., 2019b) when unique differential outcomes were administered. In Plaza et al. (2012), AD patients performed at the same level that control participants in the differential outcomes condition (5 second delay). Differential outcomes training was also effective in preventing memory decay at 1 week follow-up (Carmona et al., 2019b). As expected, recognition of the eight everyday objects pictures trained during the first phase with the NOP significantly dropped at the 1 week follow-up in the group of AD patients. However, memory retention did not significantly differ between 1 hour and 1 week follow-ups for the trained stimuli under the DOP. Thus, this study and others discussed in this review article support that the benefits of the DOP in memory are long lasting. This is an important finding since research suggests that boosting sessions are required to obtain long-lasting effects with traditional cognitive training approaches (Acevedo & Loewenstein, 2007). The finding of long-lasting effects in memory with the DOP is even more remarkable if one considers that they are observed with one single training session consisting often of a relatively small number of trials (36 trials in most of the studies discussed here). Although more systematic research is needed to investigate dose-effect relationships in differential outcome training, the evidence so far with patients suffering from dementia suggests that it may be a potent intervention tool. That is, an easy-to-implement procedure that does not require extensive duration to obtain robust effects. The positive results with the only study so far that included people diagnosed with MCI are also very encouraging given that this is a relatively recent clinical construct that refers to a stage in between healthy aging and early dementia (Petersen, 2016). Therefore, any intervention that enhances cognitive function in MCI has the potential to delay or prevent the onset of dementia. Longitudinal studies using the DOP in people with MCI are needed to understand how this type of training may affect conversion rates, particularly in the amnestic type of MCI which has been more closely linked to dementia (Arnáiz & Almkvist, 2003; Petersen et al., 1999).

Differential outcomes training seems to be particularly relevant and useful to clinical populations like dementia, whose core impairment is memory and therefore patients are less able to use a retrospective route to process and retrieve stimuli in order to decide what is the correct response amongst different options. This difficulty may become more obvious when there is a long interval between the encoding of the stimuli and the response decision, or when the stimulus encoding/processing is hard (e.g., presence of distraction). In these populations, effects from training with differential outcomes seem to result from the activation of compensatory brain mechanisms. As suggested by animal (e.g., Savage, 2001) as well as neuroimaging human studies (Mok, 2012; Mok et al., 2009) discriminative learning of multiple associations and delayed memory recognition under the DOP would bypass the hippocampus and activate cognitive and neurobiological routes that are less affected in MCI and dementia. Yet, training with the DOP may be an effective intervention tool in many other clinical populations. It is widely accepted that explicit learning and memory are more vulnerable than implicit learning and memory to neurological damage (Reber, 2008). We also know that the DOP utilizes an implicit learning route, as opposed to an intentional recall of the stimulus to be learned. Thus, the DOP in conditional discriminative learning tasks may be an optimal approach to teach new skills to individuals with intellectual disabilities (e.g., Estévez et al., 2003 with children and adult with Down syndrome) and those who are less able to learn through explicit instructions due to neurological damage (e.g., see Joseph et al., 1997 with Prader-Willi syndrome; and Malanga & Poling, 1992 with people with mental disabilities). More research is needed to investigate the effectiveness and usefulness of the DOP in other neurological and clinical populations. For instance, the DOP may be particularly useful for patients with attentional problems (e.g., patients diagnosed with schizophrenia), since differential outcomes effects are greater in magnitude and more robust with cognitively challenging tasks that load the cognitive system.

Applications of the differential outcomes procedure to adherence to medical treatment

Even though in the last three decades a growing number of studies have demonstrated that the DOP can be beneficial to improve discriminative learning and visuospatial recognition memory in humans, this procedure was just recently applied to a public health concern that affects many people worldwide. We refer to the lack of adherence to treatment (WHO, 2003), which could happen at different phases of the therapeutic process (e.g., the initiation or the implementation of the treatment). It should be noted that about 50% of patients with chronic disease fail to comply with the planned prescriptions from the healthcare providers in developed countries (Fernandez-Lazaro et al., 2019). Therefore, non-adherence is a major problem that is associated with an increased risk of adverse clinical events, hospitalizations, mortality and with higher cost to the healthcare system (Bosworth et al., 2011; Sokol et al., 2005). Importantly, this risk is greater in older people as compared to younger patients (Walsh et al., 2019).

Many studies, including a recent report in the Lancet (Feigin et al., 2020), have highlighted how many societies around the world, particularly those that are more economically developed, are rapidly aging, a phenomenon known as the "*demographic change*". According to the last report of the World Health Organization, the world's population aged 60 years or more was about 900 million and it is expected to reach 2 billion by 2050 (WHO, 2022a). Although the longer life expectancy is a positive thing, the other side of the coin is that aging is associated with multiple medical problems including cardiovascular diseases, cancer, diabetes, chronic obstructive pulmonary diseases, dementia, and other degenerative conditions (WHO, 2022b). As reported by Divo et al. (2014), multimorbidity is more prevalent with age and requires multitargeted treatments (Yarnall et al., 2017), resulting in polypharmacy. It is estimated that currently 50% of the elderly people need to take 5 or more drugs while 10% of them 10 drugs or more (Delshad et al., 2005, Midão et al., 2018; Onder et al., 2014). Because of the multimorbidity associated polypharmacy, older adults are highly susceptible to non-adherence to prescriptions (Pérez-Jover et al., 2018). Added to multimorbidity and polypharmacy are patient-related factors, as forgetfulness or poor understanding of medication instructions, which may contribute to suboptimal medication adherence (Brown & Bussell, 2011). Regarding forgetfulness, it is not surprising that elderly people have more difficulties in retaining and following medical recommendations due to the age-related episodic memory (e.g., Nyberg, 2017) and working memory capacity declines (Cavanaugh & Blanchard-Fields, 2006) which hinder the patient's ability to correctly manage multiple drugs.

Thus, an important healthcare challenge is to ensure good adherence in this population so that they can receive maximum therapeutic benefits (Yap et al., 2016). Given that many factors influence adherence, there is no single solution to this problem, which requires a multidisciplinary approach (Jose & Bond, 2021). Still, it is essential to design and implement educational and behavioral interventions to prevent nonadherence to treatment (e.g., Costa et al., 2015). It is in this context where the DOP has been explored as a possible therapeutic technique to improve memory for medical recommendations, a prerequisite for a correct adherence to treatment. In a first study, Molina et al. (2015) simulated the memory burden that a polypharmacy situation imposes to those patients with multiple morbidities. Specifically, young participants had to learn and retain in their memory a new pharmacological treatment involving six pills associated with six health disorders. To assess the possible beneficial long-term effects of the DOP, participants were scheduled for two memory tests 1 hour and 1 week after completion of the learning task. One group (DOP) received specific outcomes following their correct responses during the learning phase. That is, each to-be-learned and remembered pill-disorder relationship was associated with a unique outcome. For the other group (NOP), correct responses were also reinforced but the outcomes were randomly administrated. The results showed both improved learning and long-term retention of the learned information when differential outcomes were arranged.

Later on, these findings were extended to older adults and people diagnosed with Alzheimer disease (AD) handling medication prescriptions (Molina et al., 2020; Plaza et al., 2018). Regarding elderly people, Plaza et al. (2018) investigated the effectiveness of the DOP to improve learning and long-term retention (1 hour and 1 week) of associations between hypothetical prescription drugs (blue, yellow and blue pills) and time of administration (early in the morning, midday and night) in a group of cognitively healthy younger and older adults. Participants were randomly assigned to the DOP or the NOP conditions, and pictures with positive valence along with the sentence "you may win a … (a gift as a *primary reinforcer*)" were presented as outcomes. As expected, the effect of differential outcomes manipulation with accuracy and latency data was only observed for the older adult group, and the two effects were of a large size in line with the meta-analysis of McCormack et al. (2019). Furthermore, in the DOP group, older adults' performance with both accuracy and latency data did not differ from that of their younger counterparts. The DOP was also effective in improving long-term retention (1 hour and 1 week) of the learned associations but only in the older adult group (large effect size). Most important, while in the NOP condition memory retention was overall worse for older adults relative to younger adults, the two age groups did not differ in long-term retention under differential outcomes arrangement.

Finally, in a recent follow-up study, Molina et al. (2020) investigated the effectiveness of this procedure to enhance learning and retention of information related to medical treatment in older adults diagnosed with AD. The procedure used here was similar to that from Plaza et al. (2018) except that the number of pills was reduced to two and there were two training sessions separated by two days preceded by a pre-training session. AD patients showed better performance in the DOP condition only in the second training session. This finding suggests that the amount of training is a key factor when working with this population. Importantly, the benefit of the DOP extended also to the memory tests. In fact, AD patients learned and remembered the pill/time of day association only when differential outcomes were arranged, being their performance at chance level in the NOP condition. Taken together, the findings from these three studies highlight the potential of the DOP to facilitate learning and retention of medical recommendations (e.g., the time-based schedule of the medication administration) in different populations.

Based on the results obtained in these three studies, researchers from different countries, led by researchers from the University of Almería (Spain), are currently working on a research project whose main aim is to design a free and easily accessible app tailored to older adults that implements the DOP to improve the learning and recall of crucial information related to adherence to treatment. We refer to the disorder-treatment or time of day-treatment associations (understanding the treatment as the type of medication or supplement and time of day as the time of treatment intake). The app consists of two types of trials, one for each of the associations to be trained. The correct response on each trial is followed by a specific outcome. Thus, for example, whenever the patient correctly chooses that the red pill is taken upon getting up, the photograph of a landscape will appear (see Figure 3, section A). That same photograph will also appear when they correctly indicate that the red pill was prescribed for treatment of cholesterol, and never for any of the other treatments (see Figure 3, section B). Before starting the training, the users of the app will enter data of their medication (the name and a photograph) and the disease associated with it. They also will choose the associated outcomes from a group of pictures available in the app or by taking themselves a picture of something they like. Once its effectiveness has been established, this app could be included as a complementary technique in intervention programs targeted at increasing adherence to clinical recommendations fostering, at the same time, that the elderly people play an active role in dealing with their diseases.

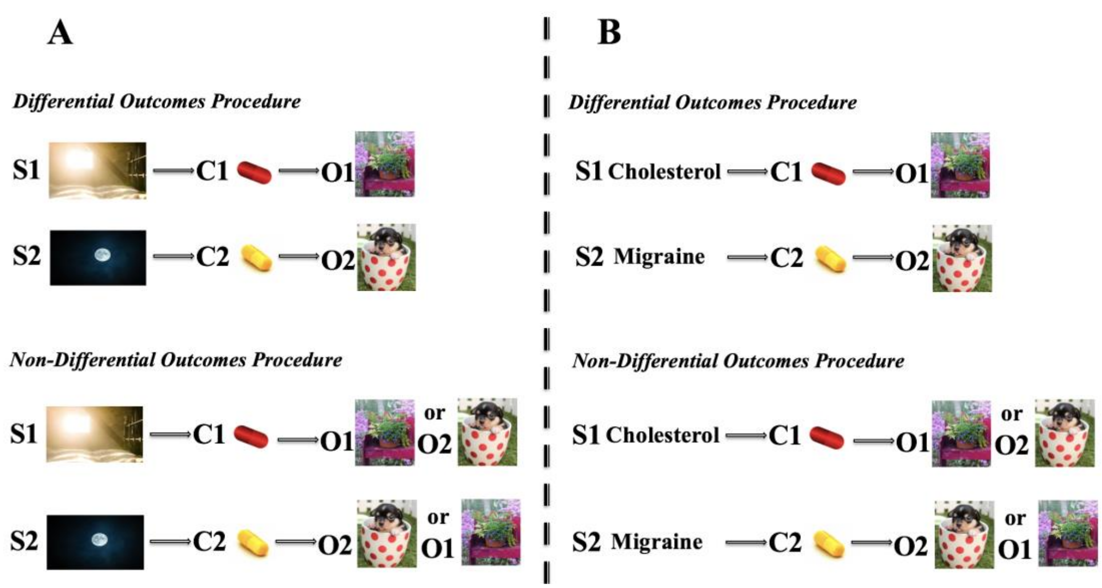

Figure 3. Example of the time of day-treatment or disorder-treatment associations trained with the DOP or the NOP. In the app only the DOP is shown. S=sample stimulus; C=comparison stimulus; O=outcome.

Following this project, other apps could be designed in the future to improve other fundamental cognitive processes for daily life, such as the recognition of emotional facial expressions. In a recent study, González-Rodríguez et al. (2020) found that the DOP enhanced this type of recognition memory in healthy adults. Although further research is needed, this finding is very relevant for clinical practice as the use of this procedure might specially help those people with problems recognizing emotional facial expressions, such as people diagnosed with schizophrenia or autism spectrum disorder. We consider that the DOP might be easily adapted to be used in clinical contexts that promote health. Undoubtedly, the implementation of this procedure in apps for mobile devices opens up a future of possibilities with respect to its possible applications.

Conclusions and future directions

In this review article we aimed to show how a procedure developed within the domain of basic science can become a useful tool in applied science, specifically in the fields of education and health. The DOP has provided a link, albeit unintentionally, between researchers from different disciplines within the field of psychology, including learning, memory, perception, and attention as well as from other disciplines such as medicine and the industry (technology developers), which can lead to research outputs with potential impact. Therefore, the DOP is a good example of interdisciplinary collaboration. Animal learning researchers explored various procedures to accelerate and improve discriminative learning, looking not only at the final learning outcome, but also at the associative mechanisms involved in such learning procedure. It soon became apparent the enormous potential that the DOP could have both in the field of human learning and in the applied fields of education and health, as a useful intervention tool to optimize and improve learning in children and clinical populations. The potential of the DOP went beyond the field of learning and extended to the field of memory, where it was shown that delayed memory recognition and long-term retention was improved under the DOP. There is now substantial research that supports DOP advantages both in learning and memory. In the future we hope that the DOP will leave the laboratory and become a useful tool to improve the autonomy of our elderly in important aspects such as health. The multi-pathological conditions that afflict many of our elders require useful strategies to help overcome the enormous burden on working memory of dealing with disease-treatment associations that is at the root of the problems associated with adherence to medical treatment. The next step concerns transnational science. New digital communication technologies open the door to further advances in the use of the DOP in more applied contexts as it has been discussed in the present review. It is a development that is just around the corner and for which we hope new researchers in the health field will join in this exciting enterprise. We are sure the Spanish Society of Experimental Psychology will play an essential role in promoting such an endeavor.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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