Working memory training:

Taking a step back to retool and create a bridge between clinical and neuroimaging research methods

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Improvements in patient outcomes and mortality after brain injury alongside increasing ageing population have resulted in an increasing need to develop cognitive interventions for individuals experiencing changes in their cognitive function. One topic of increasing research interest is whether cognitive functions such as attention, memory and executive functioning can be improved through the use of working memory training interventions. Both clinical and neuroimaging researchers are working to evidence this, but their efforts rarely come together. We discuss here several issues that may be hindering progress in this area, including the tools researchers utilise to measure cognition, the choice between employing active or passive control groups, the focus on transfer effects at the expense of well-characterised training effects, and the overall lack of neuroimaging studies in individuals with neurological disorders. We argue that the only way to advance the field is to build bridges between the disciplines of clinical neuropsychology and cognitive neuroscience. We suggest a multi-level framework to validate the efficacy of working memory interventions and other forms of cognitive training that combine both clinical and neuroimaging approaches. We conclude that in order to move forward we need to form multidisciplinary teams, employ interdisciplinary methods, brain imaging quality rating tools and build national and international collaborations based on open science principles.

Keywords: *brain injury, neuropsychological rehabilitation, cognitive training, working memory, neuroimaging*

In recent decades life expectancy has increased across the globe (Oliver et al., 2014). At the same time, patient outcomes and mortality rates from acquired brain injuries (ABI) such as stroke and traumatic brain injury (TBI) have improved (Feigin et al., 2014; Lawrence et al., 2016). As a result, there is a growing proportion of the population experiencing long-term changes in their cognitive function from ABI or experiencing cognitive decline due to ageing even in the absence of disease (Andrews-Hanna et al., 2007; Bishop et al., 2010). Neurodegenerative disorders can also be a cause of cognitive decline and there has been a plethora of research on developing pharmaceutical (Heiss et al., 1994; Loewenstein et al., 2004) and behavioural (Marshall et al., 2011; Tárraga et al.,2006; Hill et al., 2017) interventions in that context. However, this review will concentrate on research addressing the cognitive impairments resulting from ABI. Cognitive impairments impact upon everyday functioning and can turn previously simple activities of daily living (ADL), such as cooking, shopping and using public transport, into hazardous tasks (Chung et al., 2013; Galetto & Sacco, 2017; Krasny-Pacini et al., 2014). There is therefore a need for effective rehabilitation interventions that address the cognitive deficits arising from ABI or ageing to enable people to lead independent, fulfilled lives.

In neuropsychological rehabilitation there is a strong emphasis on supporting people to become independent in ADL. One domain of cognition that is critical for effective independent living is executive functioning – which refers to the ability to problem-solve, to plan, and manage tasks effectively. Clinical guidelines in relation to the rehabilitation of executive functioning following ABI recommend the use of 'meta-cognitive strategy training' (Ponsford et al., 2014; Tate et al., 2014; Velikonja et al., 2014). Meta-cognitive strategy instructions focus on encouraging the individual to 1. set goals, 2. break the task/goal down to smaller sub-tasks/goals, 3. regularly bring their attention back to the task/goal at hand and 4. actively monitor their performance. This has informed the development of a standardised and validated tool called Goal Management Training (GMT) (Levine et al., 2000; 2011). The overall efficacy of meta-cognitive strategy instructions has been investigated in several randomised controlled trials (RCTs) including adults suffering from executive dysfunction (Levine et al.,

2000; McPherson et al., 2009; Rath et al., 2003; Spikman et al., 2010; Stamenova & Levine, 2018) as well as problems with memory (Kaschel et al., 2002; Ryan & Ruff, 1988; Shum et al., 2011) and attention (Fasotti et al., 2000). The use of environmental supports such as external memory aids and reminders, e.g. mobiles/smartphones, notebooks, virtual digital assistants, have also been evaluated in RCTs (Fish et al., 2011; Wilson et al., 2001) and is clinically recommended for use with adults who have memory difficulties (Velikonja et al., 2014). These types of strategy-based interventions, familiar to many clinical neuropsychologists, are classified as 'compensatory' (compensating for impairments of cognitive functioning through the use of external aids or instructed strategies).

Researchers in the field of cognitive neuroscience, however, have been interested in process-based interventions that are often characterised as 'restorative' (aiming to restore to normal, or near-normal, underlying core cognitive processes including executive functions) (Brehmer et al., 2014). Consequently, there has been increasing research interest among cognitive neuroscientists in the development and evaluation of computerised cognitive training process-based paradigms. These have been utilised in two different contexts: 1. for "boosting" healthy young and older adults' cognitive function (Au et al., 2015; Brehmer et al., 2014; Brehmer et al., 2011; Jaeggi et al., 2008; Lampit et al., 2014) and 2. for cognitive rehabilitation in individuals with neurological damage such as ABI (Bogdanova et al., 2016; Galetto & Sacco, 2017; Hallock et al., 2016), dementia and mild cognitive impairment (MCI) (Gates et al., 2011; Hill et al., 2017; Sherman et al., 2017). The availability of non-invasive human neuroimaging methods (such as Magnetic Resonance Imaging, MRI) has contributed to the popularity of cognitive training research in cognitive neuroscience, enabling the measurement of experience-dependent changes in brain structure and function from experimentally controlled interventions.

A large number of cognitive training paradigms have been employed in both clinical and neuroimaging research studies, with working memory (WM) training regimes being the most popular and extensively examined to date (Backman et al., 2017; Buschkuehl et al.,

2014; Clark et al., 2017; Dahlin et al., 2008; Finc et al., 2020; Flegal et al., 2019; Heinzel et al., 2016; Kühn et al., 2013; Miro-Padilla et al., 2018; Salminen et al., 2016; Thompson, et al., 2016). According to the influential three-part WM model (Baddeley & Hitch, 1974), the phonological loop and the visuospatial sketchpad are two slave systems responsible for the storage of verbal and visuospatial information, respectively; whilst the central executive component is considered to be a cognitive control system that allocates attentional resources and is necessary to support executive processes such as planning, inhibition, problem-solving, organisation, shifting, maintenance and updating. Given the WM system's involvement in complex cognitive tasks, goal-oriented behaviour and regulation of executive processes, as well as its relationship with cognitive constructs such as fluid intelligence and language comprehension (Wiemers et al., 2019), researchers have hypothesized that training WM processes can result in cognitive improvements extending beyond the specific task participants trained on, and thus represents an important target for intervention.

In the WM training literature, emphasis is placed on measuring the size of training and transfer effects in order to draw conclusions about the success of a training protocol. The training effect refers to performance on the task participants train on, also known as the *criterion* task; while the transfer effect refers to performance on an untrained task following training, i.e., transfer of learning. Transfer effects can be further subdivided into *near* transfer of learning (i.e., performance improving on an untrained task that is superficially different to the criterion task but shares the same trained WM process) and *far* transfer of learning (i.e., performance improving and/or generalising to an untrained task in a different cognitive domain such as general intelligence). This leads to one of the most controversial and debated topics in this field. Some researchers support the idea that far transfer to general intelligence tasks is possible following WM training (Au et al., 2015), and cite improvements on measures of cognitive function as showing the potential of WM training for clinical application (Weicker et al., 2016). Others argue there is no convincing evidence for the generalisability of any training effects beyond the specific tasks on which participants train and are sceptical as to whether far transfer could occur (Melby-Lervåg et al., 2016; Soveri et al., 2017), therefore questioning

the value of cognitive training for improving performance on activities of everyday living (Melby-Lervåg et al., 2019). One issue behind this fundamental disagreement is that there are inconsistencies in the way researchers categorise near and far transfer effects across studies, and therefore the existence of transfer ultimately depends upon researchers' subjective classification of what constitutes near and far (Barnett & Ceci, 2002; Pappa et al., 2020). Secondly, cognitive neuroscientists rarely -if ever- include outcome measures to assess improvement in ADL following WM training (Pappa et al., 2020), whereas in a clinical setting, the ultimate goal is for individuals to improve in ADL after completing cognitive rehabilitation. Consequently, even if we accept that transfer of learning is possible, what would this mean for cognitive rehabilitation? Would we expect significant improvements in ADL following WM training; and if so, would we categorise this as near or far transfer of learning? Naturally, that would depend on the specific ADL. For example, it could be argued that improvements in shopping and cooking activities following WM training would provide evidence for near transfer, based on the demand those tasks place upon WM processes, while improvements in managing one's own finances would likely be categorised as far transfer. One reason for the spotlight on transfer of training is that if it is possible and we find a way to understand its mechanisms, the circumstances under which it occurs, as well as for whom, then we should be able to facilitate this transfer. This has potential to be a game changer in clinical neuropsychology, and to revolutionise the way we think about cognition and cognitive rehabilitation. Alas we are not there yet.

To date, WM training research has included paediatric and adult populations, both healthy and those with clinical conditions, and employed a wide variety of training paradigms. Although most neuroimaging studies are conducted with healthy adults, vast differences between studies relating to important training task features such as stimulus modality, training adaptivity (i.e., difficulty of the trained tasks adapting to the individual's changing performance), and protocol length, together with the use of various measurements of training efficacy, have made between study comparisons extremely challenging (Pergher et al., 2020). Therefore, drawing clear conclusions on the efficacy of WM training in healthy adults has been

difficult so far. The translation of cognitive neuroscience research to clinical applications is further impeded because training studies using neuroimaging outcome measures rarely include adults with neurological disorders, assess ADL outcome measures nor follow gold standard RCT methodologies (Galetto & Sacco, 2017; Pappa et al., 2020). In addition, currently there are no tools to specifically assess the methodological quality of neuroimaging training studies (Pappa et al., 2020) comparable to the many tools for evaluating randomised controlled study designs (e.g. the PEDro-P scale – Maher et al., 2003; Sherrington et al., 2000). We can only presume the reason for the lack of neuroimaging-related quality assessment tools is directly related to two main points: 1. the overall lack of training-related neuroimaging studies with neurological samples; and 2. the small number of clinical rehabilitation studies including neuroimaging methods. To put it simply, the need for having such tool has not emerged yet.

This short introduction has focused on the complexities behind the controversial and intriguing field of cognitive training research with a specific focus on WM training. We argue that one of the most important causes for the inconsistencies in training efficacy results is the lack of convergence between studies utilising neuroimaging outcomes and studies that focus on clinical methodologies. There are significant practical challenges in conducting both neuroimaging-focused studies (e.g., scanning costs, access to qualified radiographers) and clinically-focused research (e.g., access to clients with neurological damage, the heterogeneity related to neurological damage and its functional impairment, the involvement of clinical staff). However, we believe there is a deeper issue that is rooted in a historical chasm between clinical and neuroimaging research. We believe that each field could benefit from the other through collaborative, rather than siloed, working. Different research fields are working towards tackling the same problem utilising methods and scientific approaches specific to their field, but we consider the only way forward is intersection, interaction and interdisciplinarity to investigate this scientific question of mutual interest; to put it simply, we need to look together at the same problem from different angles and perspectives. This review places emphasis on studies targeting WM processes due to their popularity in the field of

cognitive training research. We will discuss some key issues that need to be taken into consideration in order to advance the field. In addition, we will focus in particular on the tools utilised by researchers to evaluate the efficacy of training and the use of complementary neuroimaging methods and analyses. Even though the present review focuses on WM, we consider these issues common across the research area of cognitive training more broadly.

Measuring cognitive performance: What are we measuring?

The need to effectively measure cognition is at the heart of psychological research whether in the field of clinical neuropsychology or cognitive neuroscience. In summarising the types of validated psychometric tools used in clinical rehabilitation settings to assess cognitive abilities, we would say there are three broad categories: 1. construct-driven, 2. ecologically focussed and 3. functional ability in ADL. The first approach refers to tests that were designed to measure specific cognitive constructs; for example, the construct of inhibition is measured by the Stroop test (Stroop, 1935); cognitive flexibility and processing speed can be assessed with the trail making test (TMT) (Reitan, 1958); planning and problem solving is measured by the Tower of London (Culbertson & Zillmer, 1998). Many such tests were devised by early cognitive neuropsychologists to examine dissociations in cognitive functions between patients with brain damage and were later adapted into clinical psychometric tools, with normative samples against which individual patients may be compared (Parsons, 2016). Recently, there have been efforts to utilise modern technology and adapt existing construct-driven tests into computerised assessments such as CANTAB (CANTAB®, 2019) and Cambridge Brain Sciences (Owen et al., 2010) software, although use of these tools in clinical settings remains limited for a variety of reasons, including their cost.

The construct-driven test approach has been criticised, however, due to the inability to effectively relate performance with everyday functioning. Consequently, many researchers argued for an approach that emphasises ecological validity and developed tools designed to be more closely related to everyday function, e.g., the Behavioural Assessment of Dysexecutive Syndrome (BADS) (Wilson, 1996) and the Rivermead Behavioural Memory Test

(RBMT) (Wilson et al., 1989). This shift from a construct-driven approach to a more ecologically focussed approach, as well as the need to conclude whether cognitive rehabilitation outcomes are meaningful in a real life context, also led to the use of validated scales assessing functional ability in ADL, e.g., the Rivermead ADL Scale (Lincoln & Edmans, 1990) and the Functional Independence Measure (FIM) (Keith et al.,1987). A systematic review on the efficacy of computerised cognitive training in ABI concluded that very few RCTs report outcomes on ADL and further emphasised the potential for employing neuroimaging methodology to better understand the mechanism behind such interventions (Sigmundsdottir, et al., 2016).

In the field of cognitive neuroscience, on the other hand, researchers mainly rely on lab-based experimental tasks to measure cognitive performance changes at a group level following training. In the WM training literature, for example, the most frequently used experimental paradigm involves the n-back task. It taxes various WM processes simultaneously such as updating, encoding, monitoring and maintenance (Jaeggi et al., 2010). The n-back task is popular for a variety of reasons: it provides a straightforward way to manipulate WM load (cognitive performance effectively worsens as load increases), it induces consistent activation in WM related brain regions (i.e., bilateral frontal and parietal areas), and performance on n-back high load levels is predictive of individual differences in measures of general intelligence and other cognitive functions (Jaeggi et al., 2010). Across studies using the n-back task there have been multiple variations of key task features such as the task modality (i.e., visuo-spatial, verbal, auditory), the number of load levels, and whether the task is presented in a single or dual modality. A major issue is that this variability in important task features, as well as other differences in the various WM training protocols, makes it very difficult to compare findings across training studies (Pergher et al., 2020).

Due to the various difficulty levels and task conditions in WM paradigms, observed enhancements in post-training performance might originate from improvement in just one level or condition of the experimental task rather than across all levels and conditions.

Consequently, researchers draw conclusions based upon performance changes where participants have improved *the most* rather than on the average across levels or conditions. When meta-analytic studies average across levels and conditions to present unbiased results and test for publication bias and heterogeneity across studies, the training related effects overall turn out to be smaller (Pappa et al., 2020). Furthermore, neuroimaging researchers seldom use clinically validated psychometric tools to measure training efficacy and when they do, performance on these tasks typically does not improve significantly (Backman et al., 2017; Biel et al., 2020; Colom et al., 2013; Thompson et al., 2013). Additionally, tests that are considered more ecologically valid or scales assessing functional ability in ADL are very rarely used in the WM training field (Pappa et al., 2020); and cognitive training field in general (Sigmundsdottir et al., 2016). As a result, these issues pose a major drawback for implementing such training regimes in a clinical setting because of difficulty ascertaining that the size of the cognitive improvement following training is accurate, clinically meaningful and/or relevant for better managing the challenges of everyday living.

Active Vs Passive Control Groups: Does it make a difference?

Central to good science in relation to the evaluation of intervention efficacy is the use of control groups (CGs) to control for effects not specific to the intervention. The two types of CGs are: 1. *active CG, i.e.* participants receive an alternate intervention, which controls for non-specific aspects of the experimental intervention, and 2. *passive CG, also known as no contact CG*, i.e. participants do not engage in any intervention. The findings across various WM training studies and meta-analyses have not been conclusive on which is the most appropriate type of CG or how this choice affects the size of the training and transfer effects. Some authors suggest the type of CG does not influence the transfer effect size (Au et al., 2020; Soveri et al., 2017) whilst others conclude that the employment of a passive CG overestimates the transfer effect (Dougherty et al., 2016; Melby-Lervåg et al., 2016). A recent meta-analysis on the effects of WM updating training found that when comparing the training group (TG) against an active CG the *training effect* is mild to moderate. By contrast, comparing

against a passive CG resulted in very large effect sizes, indicating the training effect is overestimated (Pappa et al., 2020). This inconsistency has given rise to concerns regarding training efficacy. Active CGs are methodologically stronger for determining the specific effects of an intervention but are likely to result in smaller effect sizes (as they control for non-specific effects on outcomes) and thus require substantially larger sample sizes. This has implications for clinical studies in particular since larger sample sizes can be quite challenging without substantial funding and multiple recruitment sites and teams collaborating together.

Passive CGs provide an evaluation of an intervention against no-intervention but do not control for non-specific effects (Green et al., 2014), of which there are a number. For example, outcomes from WM training could be influenced by the expectancy of improvement (i.e., due to the TG and CG being treated differently, then a larger training improvement favouring the TG might stem from the participants' expectation) and greater social contact with the experimenters (Boot et al., 2013; Shipstead et al., 2012). Therefore, researchers should work towards matching expectations of improvement in both TG and CGs (Shipstead et al., 2012). A recommendation for active CGs is creating a control task distinct enough from the training task to maximise the observable training effect (Green et al., 2014). To achieve this, some researchers have proposed the use of an adaptive difficulty training protocol for the active CG but on a different cognitive domain (Shipstead et al., 2012), e.g., adaptive WM protocol for the TG versus an adaptive processing speed protocol for the active CG. Alternatively, others have emphasised achieving a balance between a passive CG and an overly challenging active CG by employing a lower level task paradigm (von Bastian & Oberauer, 2014), e.g., adaptive WM protocol for the TG and a fixed low level difficulty WM protocol for the active CG. However, as Green et al. (2014) correctly pointed out, while devising a "standard" CG protocol across studies would be useful but probably unachievable, the optimal CG ultimately depends upon the specific research questions and study aims. For example, in a clinical rehabilitation setting, the group receiving a cognitive intervention may be compared against a "treatment as usual" CG, which may be no intervention at all. Even though theoretically this CG is not controlling for expectancy effects or other confounding

variables, it can still prove useful in assessing overall effectiveness in the early stages of a trial, or once efficacy has been demonstrated against an active CG, comparison with 'treatment as usual' provides evidence of the added benefit of the intervention in clinical practice.

Shifting the focus back on to the training effect: What steps are needed?

WM training researchers from either a clinical or neuroscience background measure participants' performance at (at least) two time points, i.e. before and after the training interval. In addition to performance changes on the training task, a number of transfer tasks are usually included to assess near and/or far transfer of learning following WM training. As introduced above, near transfer of learning refers to improved performance on an untrained task of the same domain, while far transfer refers to improved performance on an untrained task of a different cognitive domain. For this reason, research studies very frequently measure the success of a training paradigm based on whether transfer occurred and therefore, researchers are particularly interested in the existence, nature and size of the transfer effect. However, studies focusing on developing and validating any cognitive interventions rarely find large effect sizes, especially on measures of everyday functioning. This finding is consistent with clinical trials of medications where improvements in cognitive function and ADL tend to be small when compared against a placebo (Birks et al., 2015). Therefore, if the training effect itself is likely to be moderate, especially when comparing the TG against an active CG (Pappa et al., 2020), this raises questions regarding whether transfer of training effects can be anything other than small, and therefore only detectable in adequately powered studies with very large sample sizes. One way to address this is to break-down the experimental process into smaller steps, or phases, an approach that is consistent with the MRC Guidelines on developing and evaluating complex interventions to improve health (Craig et al., 2008). To adapt this approach to streamline the evaluation of cognitive training studies, we suggest the following three stages:

Stage 1: Small-scale feasibility studies to assess delivery of the intervention, bring together data on drop-out rates, sample size, recruitment, outcome measures etc. Both active and passive CGs would be informative at this stage. RCT methods are not essential when investigating all aspects of feasibility, but pilot studies that look at feasibility of running an RCT are important options. Statistically significant training effects are not expected due to small sample sizes while neuroimaging methods are not essential at this stage. It could be that a number of small-scale feasibility studies may be required to refine the study design before progressing onto Stage 2. In cases of multiple refinements, the later ones should be as close to a larger trial in design as possible.

Stage 2: A well-controlled and sufficiently powered study with an emphasis on assessing training efficacy. Comparing the TG against an active CG in a well-controlled experimental setting is recommended. This stage is ideal for examining core training features before proceeding to the next stage. The outcome measures focus on training and transfer tasks and follow a construct-driven approach. Neuroimaging methods are essential at this stage to explore the training related neural changes and facilitate understanding of the learning mechanism.

Stage 2 could be further subdivided if the estimated sample sizes for sufficient power to detect training related effects differ for the behavioural and neuroimaging components:

> *Stage 2a Behavioural component:* a well-controlled and sufficiently powered study emphasising the efficacy of training with a specific focus on measuring the training and transfer effects following a construct-driven approach. Adding a qualitative evaluation component relating to the intervention and ADL would provide valuable information especially for studies with clinical groups, although it is not essential at this stage.

Stage 2b Neuroimaging component: a well-controlled and sufficiently powered study employing pre-test and post-test scanning sessions to explore the training related neural changes. A combination of functional and structural neuroimaging analyses could be employed.

Stage 3: Large-scale trials for evaluating the training effectiveness with an emphasis on real world conditions rather than a well-controlled experimental setting. Comparing the TG against a passive CG or "treatment as usual" might be preferrable at this stage to reflect real life settings. Researchers should select a few outcome measures with particular focus on ecological tasks, ADL alongside a key outcome used in the previous stage and may consider assessing maintenance of intervention gains and evaluating long-term cost-effectiveness. Neuroimaging methods are not essential at this stage.

Other training related factors: What else to consider?

Another issue to consider is whether training gains are influenced by individual differences, including pre-training baseline performance. Two opposing approaches to understanding this issue have been prominent so far: compensation and magnification. In the first case, compensation hypothesizes that individuals starting from low baseline level exhibit larger training gains because they have more room for improvement, through compensating for inefficient pre-training performance, whilst those with higher performance at baseline, i.e. at or close to ceiling, will benefit less because there is less room for improvement. On the other hand, magnification suggests that any pre-training differences between individuals are magnified due to training. Larger gains are predicted for those with higher cognitive performance at baseline, through employing more pre-training resources, while those performing poorer at baseline are expected to improve less due to limited pre-training resources constraining their potential to adopt and implement the trained skills and/or strategies (Lövdén et al., 2012). In fact, there is evidence in favour of compensation (Jaeggi

et al., 2011) as well as magnification (Foster et al., 2017; Wiemers et al., 2019) in the cognitive training literature.

An interesting study by Lövdén et al. (2012) employed an episodic memory training protocol with individualised mnemonic strategy instructions for the first two training sessions followed by an assessment session and then individualised adaptive difficulty training for the remaining five training sessions. The authors computed a score for instruction training gains and practice training gains and suggested that among three age groups (children, young adults and older adults), those starting at a lower baseline level compensate after instruction training and between-individual differences reduce, while continued practice exposes evidence of magnified between-individual differences with those starting at a higher baseline level benefiting more following training. Hence, the relationship between baseline performance and training gains might not be explained by a straightforward compensation or magnification approach; rather it might additionally depend upon other factors such as training type (strategy- or process-based) and difficulty level (fixed or adaptive). Examining hypotheses for a time-dependent account, i.e. during the early training period those starting off at a lower level compensate and performance differences between individuals reduce; while following training completion those with higher baseline performance benefit more and individual differences become evident; requires both early training and post-training assessment sessions.

As a further consideration regarding the temporal dynamics at play, using a combination of neuroimaging and behavioural methods to investigate the timeline in which performance gains occur throughout the training period and also shortly thereafter could further delineate the learning mechanism. A longitudinal study design with only two time-points, i.e., pre and post, might only provide a small snapshot of the training related changes in performance and neural function whereas additional assessment points allow us to construct, piece by piece, the timing in which those changes occur. For example, do individuals exhibit rapid changes early on in the training period or is there a slow and steady

growth curve? Do these training-related changes plateau after a while and thus render lengthy training periods unnecessary? Additionally, does the timing of changes depend upon individual differences such as age or baseline performance? These are all important questions that could be answered by adding more assessment points during the training period. The next question one might wish to answer is, are training-induced changes maintained over time? Once again, the nature of the research question determines the exact time-point when the additional post-training assessment session(s) should be conducted. One final question that is of particular mechanistic interest to us, is whether individuals with neurological disorders exhibit a learning curve similar to a control sample with the training-related changes following a similar timeline.

Since most WM training studies have been conducted in healthy adults and findings on who will likely benefit more are still inconclusive, making predictions in relation to clinical samples' response to training is challenging. Sala & Gobet (2019) raised the question of whether the training benefit might be greater for populations starting from a baseline of cognitive impairment, consistent with a compensation approach. Indeed, cognitive training studies on participants with a diagnosis of schizophrenia suggest that those starting off the intervention with the greatest impairment are more likely to benefit from it (DeTore et al., 2019; Harvey et al., 2020). On the other hand, those with milder cognitive deficits could also be predicted to benefit from a cognitive intervention by maintaining their cognitive functioning at a stable level and preventing it from worsening. This could be particularly relevant for older adults without a neurodegenerative condition who experience cognitive deterioration due to natural ageing process (Lustig et al., 2009). This intriguing issue clearly needs to be further addressed in the clinical populations of interest. Thus, once again, it is fair to conclude the field needs more training studies involving individuals with neurological disorders and participants exhibiting various levels of baseline cognitive function.

Another under-studied factor of particular interest in the training literature is motivation. It has been suggested that if a participant holds the belief that cognitive training can improve

outcomes such as intelligence, then that in itself is a motivating factor that can influence the training outcome (Katz et al., 2016). Therefore, it could be argued that an individual with a brain injury has an even stronger motivation to complete the intervention and put in extra effort to improve their performance and cognitive abilities compared to healthy controls. Then again, those with neurological injury are often unaware of their own impairment, i.e. suffer from anosognosia (Arnould et al., 2016). This can substantially hinder their motivation and willingness to engage in cognitive training and it is a factor that should be accounted for in studies including adults with neurological impairments. Therefore, motivation is of particular importance in clinical samples and should be further investigated and taken into consideration when interpreting training effects. Further to this, participants' motivation is more likely to be enhanced by knowing they will be involved in some kind of training activity as opposed to nothing, and will be an important point to consider when deciding how active and passive CGs are framed.

Furthermore, the concept of cognitive reserve (CR), i.e. the hypothesis that certain individuals are more resilient to brain damage (Stern, 2002), is also relevant. The factors associated with CR could relate to the individual's level of education, occupational attainment, amount of physical exercise as well as social stimulation; and thus information related to these should ideally be collected (Stern, 2012). Baseline cognitive performance, motivation, presence of anosognosia, severity of cognitive deficit and CR are key factors that could be influencing the individual's response to training and should be taken into account in studies with neurological samples.

Combining neuroimaging analyses

Most cognitive neuroscientists employ functional MRI (fMRI) to examine changes in patterns of brain activity induced by WM training and therefore research studies presenting findings from other neuroimaging modalities, such as training-related alterations in brain structure and functional connectivity, are disproportionately fewer. Even though there is inconsistency across studies in the direction of functional activity changes following training,

a recent meta-analysis identified a more homogeneous training-related pattern of activity *reductions* and attributed this to focusing on studies that trained the specific process of WM updating (Pappa et al., 2020). Unfortunately, as yet there are too few studies exploring other brain MRI modalities (e.g., volumetric or surface-based morphometry and network measures of connectivity within and between brain regions involved in the learning process) to draw any conclusions on training-induced changes, as noted in the meta-analysis by Pappa et al. (2020) and another review focusing on executive function training in older adults (Nguyen et al., 2019) where only four of the twenty studies employed structural imaging analyses.

Examining the functional activity response following training undoubtedly gives an important insight into the neural workings of learning but fMRI analysis alone is not sufficient to understand the underlying mechanisms. It could be that the subtle changes following training, as exhibited by moderate behavioural training and transfer effect sizes, are more reliably captured by analyses of functional connectivity which would instead give an indication of the neural changes at the network level rather than within separate brain regions. Along the same lines, positron emission tomography (PET) is an alternative neuroimaging methodology that enables researchers to investigate the function of neurotransmitter systems. This can provide invaluable converging data on the mechanism of learning due to the link between dopaminergic neurotransmission, for example, and functional activity in the WM related striato-frontal brain areas understood to be involved in the mechanism of learning (Bäckman et al., 2011).

That is not to deny the suitability of fMRI analysis for exploring neural changes following training; it is just to highlight that valuable information is missing if additional complementary analyses are not used. Similarly, if we hypothesize that a short WM training regime is not sufficient to produce significant volumetric brain changes in conventional structural MRI analysis, as exhibited when acquiring new visuo-motor skills (Draganski et al., 2004; Taubert et al., 2010) or following a longer learning period (Draganski et al., 2006), then employing diffusion tensor imaging (DTI) to examine training-related changes in the

microstructural integrity of white matter tracts might be a more effective method to delineate the learning mechanism. The point here is that employing more than one neuroimaging analysis for the same dataset can give a more complete picture of the neural process of learning and thus enable researchers to draw more consistent conclusions. The combination of different neuroimaging analyses to fully investigate the neural mechanisms involved in WM training could be equated to evaluating the effectiveness of a training intervention using different types of quantitative measures (i.e., construct-driven, ecologically focussed or functional ability in ADL) in quantitative behavioural studies or likened to mixed methods evaluations utilising both quantitative and qualitative measures (e.g., qualitative interviews of participant's perceptions or experiences in addition to quantitative measures).

Finally, even though there are disproportionately more studies investigating the pattern of training-related changes in fMRI activity than employing functional connectivity and structural imaging analyses, still the most considerable oversight in the field is the lack of neuroimaging studies on neurological samples overall. In their systematic review, Galetto & Sacco (2017) identified only eleven published studies that employed neuroimaging and neurophysiological methods in individuals with TBI. The authors were unable to draw meaningful and consistent conclusions due to the very small number of included studies, the heterogeneity amongst the training protocols in terms of the trained cognitive function, the absence of CGs in many cases, as well as the small sample sizes. Despite these limitations, however, the authors suggested that cognitive training can successfully promote neural modifications in individuals with brain injury. Another systematic review with a specific focus on WM updating identified only four published studies employing neuroimaging methods in people with neurological damage. Once again, these either had small sample sizes, did not include CGs or were case studies, and therefore reaching meaningful conclusions was not possible (Pappa et al., 2020). These reviews highlight that the need for neuroimaging studies in clinical samples is apparent. Their inclusion is absolutely necessary if we want to move the field forward.

How do we move forward?

Cognitive Neuroscientists & Clinical Researchers

Even though this review focused on studies employing WM training protocols, the proposed suggestions could prove useful for a variety of cognitive processes and training protocols. Therefore, we suggest that researchers interested in conducting cognitive training studies overall -and not limited to WM- should consider some key issues before starting data collection. To begin with, there is a move towards open science and research practices, so scientists are encouraged to pre-register their studies, including the proposed research questions, hypotheses, and intended data analysis before commencing data collection via published pre-registered reports, trial protocols and registrations or via open-science platforms such as the Open Science Framework (OSF) and PROSPERO the International prospective register of systematic reviews. We believe peer reviewing research at the very early stages is the optimal way to minimise publication bias, improve experimental design and promote high quality research as well as national and international collaborations. At the same time, employing systematic reviews and/or meta-analyses of previous research is a useful first step to gaining a deeper understanding and knowledge of the field, its limitations, and omissions.

In terms of experimental design, aiming towards including more adults with neurological disorders in neuroimaging studies would be a major contribution in this field and a step closer to increasing the translation of research into clinical practice. With the exception of very early feasibility development, randomised controlled trial methods should be used with an active CG to control for expectancy effects, selecting CG task features fitting the specific research question and exploring motivating factors for completing the training. In terms of outcome measures, reporting averaged scores if there are multiple experimental conditions or multiple tasks assessing the same cognitive function, similar to meta-analyses methods, enables more accurate and unbiased training and transfer effect sizes to be obtained. Further to this, including additional assessments throughout the training interval enables us to examine how training-related changes develop over time. Naturally the next step would be to

investigate whether those training gains extend beyond the end of the intervention and for this a follow-up assessment post-training is necessary. A closer look into how individual differences impact training gains, how the timeline of those changes emerges and whether these are preserved beyond the end of the intervention will be important for informing clinical guidelines. Finally, devising tools to assess the quality of neuroimaging training studies would be very useful for bringing standard practices closer together for cognitive neuroscientists and clinical researchers.

Understandably, a combination of psychometric tools, lab-based experimental tasks, scales measuring ADL and neuroimaging methods is not often feasible within a single study. Alternatively, we suggest following a three-stage programmatic approach to evaluate different aspects of the training protocol and focus on one component at a time. Adapting the MRC guidelines on developing complex interventions (Craig et al., 2008) to cognitive training research, the first stage could involve a small-scale feasibility study aiming to integrate valuable information on recruitment, drop-out rates, sample size and outcome measures. Multiple small-scale studies may be needed to further refine the study methods. The second stage would involve a sufficiently powered study measuring the training efficacy in a well-controlled experimental design and setting together with, or followed by, the employment of neuroimaging methods to investigate the neural learning mechanism. The final development stage focuses on measuring the effectiveness of the training intervention in real world conditions and involves a combination of ecologically valid tasks and ADL measures. Employing these steps on a linear trajectory is not a necessity; and each step has a role to play in informing and modifying the others. The ability to adapt the training protocol throughout the various stages while keeping in line with external factors such as funding resources, timelines, stakeholders etc. is an equally important aspect of the process and should not be neglected.

Research design practices aside, there are other issues to consider that could improve the way we conduct cognitive training research. Greater use of functional neuroimaging

methods and analyses in neuropsychological rehabilitation settings could reveal clinically valuable information that would otherwise be missed, e.g., neural patterns of activity and connectivity post-injury. The combination of multiple methodologies both within and across the disciplines of cognitive neuroscience and clinical neuropsychology presents a unique opportunity to develop rich datasets with information on individuals' cognitive abilities, relationship between brain structure and function, response to cognitive training and/or rehabilitation, mental health history, demographics and clinical diagnosis. Further to this, utilising open science platforms and pooling data from multiple organisations will accelerate research progress. We can then integrate these data to build models to predict an individual's response to therapy and identify which factors have the biggest role to play. These models can potentially account for individual differences and assist clinicians in devising individualised and optimal rehabilitation regimes. We acknowledge that such an endeavour would be very expensive and in need of neuroimaging expert members of staff within health service organisations, though this does not mean we should not be actively working towards this as our end goal.

Health Organisations, Regulatory & Funding Bodies

Naturally, researchers themselves cannot progress unless they are supported by the associated health organisations and funding bodies. One of the reasons for the lack of neuroimaging studies including people with neurological disorders is perhaps because the data governance and ethical review processes are often stricter and lengthier than for healthy populations. However, we think researchers should be actively encouraged to conduct cognitive training studies with a translational aspect, and this should be reflected in the relevant regulations and policies. Partnerships between health organisations and academic institutions could help to support the intersection of clinical neuropsychology and cognitive neuroscience research, with a particular focus on federated data systems that strictly protect patient identifiable information. At the same time, funding bodies should urge award recipients

to conduct multidisciplinary work, employ interdisciplinary methods and collaborate with other research groups, both nationally and internationally. A similar approach should be followed by academic institutions themselves by promoting and assisting early-stage researchers to visit and work in other research settings. Even if physical presence is not possible due to mobility problems, limited project finances, personal caring responsibilities or any other reason, recent circumstances have demonstrated that this is not an obstacle that cannot be overcome (Holmes et al., 2020; Spagnolo et al., 2020). Connecting with other researchers by sharing datasets and discussing analyses can be achieved remotely and facilitated with the use of decision-making flowcharts. Nowadays, we can access data any time, from anywhere in the world and it would be a shame not to take advantage of this extraordinary opportunity. A few examples of exciting initiatives promoting collaboration and multidisciplinary approaches relevant for cognitive training and cognitive rehabilitation studies are 1. the International initiative for TBI Research (InTBIR) (Tosetti et al., 2013) with a focus on collecting, standardizing, and sharing clinical data for comparative effectiveness research, 2. the Medical Informatics Platform with an aim to create a bridge between brain-science and clinical research and patient care, as part of the EU-cofunded Human Brain Project https://www.humanbrainproject.eu/en/medicine/medical-informatics-platform/ and 3. the International Neuroinformatics Coordinating Facility (INCF) with a mission to develop, evaluate and promote best research practices, open science and reproducibility https://www.incf.org/about-incf.

To conclude, we recognize these recommendations cannot be employed by everyone and/or all at once. However, we want to place emphasis on the unique opportunity to capitalise the knowledge, information, and technology we already have by promoting the formation of multidisciplinary teams and employment of interdisciplinary translational research projects and analyses. There is a need for bridging clinical and neuroimaging research methods in order to develop effective rehabilitation interventions for cognitive impairment – while also expanding knowledge about functional organisation of the human brain and its capacity for experience-dependent reorganisation. Through intersection, interaction and interdisciplinarity, the field of

cognitive training research can be substantially and more rapidly advanced with more researchers working together towards tackling the same problem.

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