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# Chapter 11

# DEVELOPING A QUANTITATIVE TEST OF MEMORY-RELATED MILD COGNITIVE IMPAIRMENT IN INDIVIDUALS

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**ABSTRACT**
The ability to quantify a developing memory related cognitive deficit in individuals is paramount. This becomes increasingly significant with modern society's growing aged population, who are at greater risk of developing memory deficit. In conditions such as Alzheimer's disease, early detection has significant implications for the quality and outcome of treatment. Quantification of deficit also has implications for a range of scenarios where its assessment is important in judging a patient's suitability for further treatment. Many of the current clinical tests for cognitive deficit are relatively insensitive, and struggle in individual measurements to differentiate between deficits in performance associated with learning impairment and those associated with increased rates of forgetting. We therefore argue that new tests are required that are better suited to this purpose. In this chapter we report our ongoing efforts to exploit a new theoretical advancement, to develop a new test (the Warhol Task) that has the potential to meet this requirement. More specifically we report what has been uncovered about the nature of learning and forgetting across life span, the noise inherent in the test, and the impact of error rates on parameter estimates. We also discuss the usability and the clinical potential of the test.

*Keywords:* mild cognitive impairment, memory, clinical, individual assessment, Warhol Task, memory related cognitive deficit.

## 1. INTRODUCTION

The ability to quantify a developing memory deficit in individuals is paramount. In conditions such as Alzheimer's disease, of which memory deficit is a pronounced symptom, early detection has significant implications for both the quality and outcome of treatment for those patients identified. Problems in early identification are also an obstacle for our further understanding of the disease. This points to the need to identify barely-detectable symptoms; often referred to as Mild Cognitive Impairment (MCI). Quantification of memory deficit also has implications for a range of medical scenarios as widely separated as open heart surgery and sleep apnea; where its assessment is both important in judging a patient's well-being as well as the suitability of further treatment. Such tests will also have value for those experiencing anxiety simply as a result of normal age-related decline (see Bishop, Lu, & Yanker 2010).

There are known difficulties with the tests currently in use (Cullen, O'Neill, Evans, Coen, & Lawlor, 2007). Many, such as the Mini-Mental State examination (MMSE; Folstein, Folstein, & McHugh, 1975; Tombaugh & McIntyre, 1992) are relatively insensitive, and generally are only applied when serious deficit is already apparent. Their ability to detect mild cognitive impairment, which characterizes the early stages of serious conditions such as Alzheimer's (Cui et al., 2011; Meyer, Huang, & Chowdhury, 2007; Fleisher et al., 2007; Petersen & Negash, 2008), is limited, and this renders these tests more confirmatory than predictive (Grundman et al., 2004).

Furthermore, many tests do not provide quantitative measurement at a grain of analysis suitable for tracking incremental changes in performance over time from a series of observations. This would be a desirable characteristic for general practitioners that want to have a more deductive diagnostic process (De Lepeleire & Heyrman, 1999). Many of the commonly used screening tests, like the MMSE or "General Practitioner Assessment of Cognition" (GPCOG), are based on cut-off points for when a sum of scores are sufficiently low to be

indicative of some clinical concern. These same tests are highly influenced by education, social class, age, gender, and ethnicity (Tombaugh & McIntyre, 1992). These influences make cut-off points ineffective for detailed monitoring over time, particularly for tests with a small total of scores, like the MMSE, where small amounts of variability can have significant interpretive implications.

Some tests for MCI do not measure memory at all, based on the argument that most clinical screening tests overemphasize memory dysfunction in dementia, referred to "Alzheimerisation" of screening tests (Knopman et al., 2001). The reasoning for this term is because memory dysfunction is the hallmark of Alzheimer's disease. An example test is the Clock Drawing Task (CDT), which has been used for decades across many cultural contexts. Whilst it shows some capacity to discriminate between normal aging and MCI, it is largely understood to be insensitive and more confirmatory of whether the patient has moderate-severe dementia (Ehreke et al., 2009; Pinto & Peters, 2009). In this respect it shares the same insufficiency as commonly used cognitive screening instruments for MCI. We would argue a reason why memory deficit is questioned as a criterion is because current methods are not sophisticated enough to produce clinically valuable results. The lack of sophistication is further emphasized because, from a psychological point of view, most tests measuring individual performance struggle to differentiate between deficits associated with learning impairment and those associated with increased rates of forgetting.

Of course, many of the aforementioned tests continue to be used for what benefits they do bring, but we argue that new tests are required. A common virtue shared by all the tests mentioned above is that they are quick and easy to administer in the often brief and difficult scenario of a clinical consultation (Cullen et al., 2007). For this reason they are often chosen over more sensitive tests, such as the "Blessed test of Orientation, Concentration, and Memory" (Blessed, Tomlinson, & Roth, 1968). A different benefit is that many use a number of miniature tasks to target a range of cognitive faculties. For example, the "Modified Mini-Mental State Examination" and the "Cognitive Abilities Screening Instrument" (Cullen et al., 2007). Many of these tasks are classic experimental tests and have a wealth of evidence illustrating their content validity. An obvious example is the Digit Span test. Moreover this broad variety of small tests can provide data on a wide range of faculties. Despite benefits these tests are well known to be insensitive to mild cognitive impairments.

The requirements for a successful behavioral test for mild cognitive deficit (with emphasis on learning and memory components) would be sensitive, rigorously quantitative, informative on the status of cognitive faculties, and most importantly predictive. Bearing in mind the drawbacks of currently used tests we therefore argue that new tests are required that are better suited to these requirements. In this chapter we report our ongoing efforts to exploit a new theoretical advancement based on Population Dilution Theory (Lansdale & Baguley, 2008), to specifically develop a new test (the Warhol Task) that has the potential to meet this ideal.

## 2. BACKGROUND

The Population Dilution theory looks at memory not as a simple repository of facts, but as a population of discrete representations. These discrete representations preserve both basic information about the stimulus and the historical sequence by which that information was acquired. The population may also include erroneous representations. Learning is therefore represented in this theory in terms of how numerous this population is and the accuracy of the discrete representations that comprise it. Forgetting is modeled as a process in which that population is diluted by non-functional representations at a constant-rate in time. Space limitations preclude more detailed description of this theory here, but its key facility, as realized in the "Warhol Task" (described below), is that it enables the independent assessment of learning and forgetting rates in individuals in a simple task which monitors the ability to learn the sequence of common objects in an everyday setting.

## 3. METHODS

The Warhol Task and represents – in principal – this research team's current design for meeting the requirements for improved identification of memory-inclusive MCI. As a consequence the results presented and discussed in this chapter will be focused around the development of this task. The Warhol Task is so-named because the memory stimuli are familiar food cans; alluding to Warhol's famous painting. Participants are a shown a row of 16 cans on a shelf for a fixed period; currently set at 15 seconds. After a short delay filled with tasks to suppress rehearsal, participants are tested on their memory for the sequence of 16 cans. This entails interaction with a specialized test software that presents pictures of the stimuli across a set of trials. In each of these, four pictures of cans are shown, arranged in a 2x2 matrix, and the participant is required to specify the relative order in which they appeared in the stimulus sequence. This test is called the "quartet test". Over 20 such trials, it is possible to contrive a sequence of trials in which each can has been tested against every other can in the stimulus just once. Following a delay of 2 minutes, this sequence of stimulus presentation and test was repeated 3 more times to allow an assessment of the build-up of learning. Then, after 7 days, participants are unexpectedly tested in the same way, but without seeing the stimulus.

### 3.1. Data preparation

At its most basic level this procedure tests whether the patient can correctly remember whether any two cans X and Y appeared in the sequence X-Y or Y-X. This binary judgment is made on four occasions that logically lead to 16 possible patterns of correctness over the four testing cycles; for example, this can range from all incorrect (eeee) to all correct (cccc) with 14 other possible combinations in-between (for e.g. ecce, cece, etc.). With 16 cans in the sequence, there are 120 such comparisons distributed across these 16 possible learning patterns. Given the putative probability of learning a particular sequence on any given presentation, $\boldsymbol{L}$, and taking into account the possibility of correct guesses, a complex but relatively straightforward mathematical model can predict the distribution of the 120 comparisons between the 16 possible learning patterns. As a result, given such an observed distribution, we can estimate a learning rate $\boldsymbol{L}$ for that participant using standard parameter optimization methods.

Forgetting is estimated in a similar way. Within the learning model is the ability to estimate, for any learning pattern, a population of traces of total sum (C+E), where C represents the number of traces that encode the correct sequence and E the number that are in error. At elapsed time t, the Population Dilution model predicts the probability of accurate recall to be $C/(C+E+\boldsymbol{F}t)$; where $\boldsymbol{F}$ is the rate with which the population is diluted by blank traces as a function of unit time. The probability of correct recall tracks the proportion of accurate traces in the increasing population volume. Consequently, for a given value of $\boldsymbol{F}$, we can predict the proportion of any specific learning patterns observed (e.g. ecce) that will produce a correct response after a given delay and we can estimate $\boldsymbol{F}$ from those proportions actually observed after the 7 day delay. $\boldsymbol{L}$ and $\boldsymbol{F}$ estimates derived thereby represent characteristics of the individual reflecting their rate of learning and forgetting.

Readers should be reassured that, with 120 comparisons distributed between 16 possible learning patterns, and each producing an observed probability of recall after delay, the estimation of the two free parameters $\boldsymbol{L}$ and $\boldsymbol{F}$ is far from over-prescribed and that all datasets tested thus far have produced satisfactory goodness-of-fit for the degrees of freedom so defined. The mathematical models underlying the Warhol Task are both parsimonious and statistically sufficient.

## 4. LEARNING AND FORGETTING ACROSS LIFE SPAN

Fifty-two participants aged from 18 years to 78 years participated in the Warhol Task. They were screened for health issues and matched for educational attainment. Overall, the relationship between age and cognitive performance is as might be expected. That is, a small

positive correlation with increasing age and forgetting rate is observed (Pearson's PM = 0.134); as is a similar negative correlation with learning rate (Pearson's PM = -0.267). More to the point, what is striking is the intrinsic variability between individuals; as illustrated in Figures 1 and 2 for learning and forgetting rates respectively, where each point represents the estimated rate for an individual. The variance associated with age is of second order in comparison to the differences between individuals of comparable age. Overall, this work endorses the findings of Petersen, Smith, Kokmen, Ivnik, and Tangalos (1992) that learning rates decline uniformly as a function of age whereas forgetting rates remain broadly stable when levels of initial learning have been taken into account. However, what this study reveals further is how significant the appraisal of individual differences is to the interpretation of that finding.

*Figure 1. Parameter estimates of an individual's Learning rate derived from Population Dilution model for each individual plotted as function of age.*

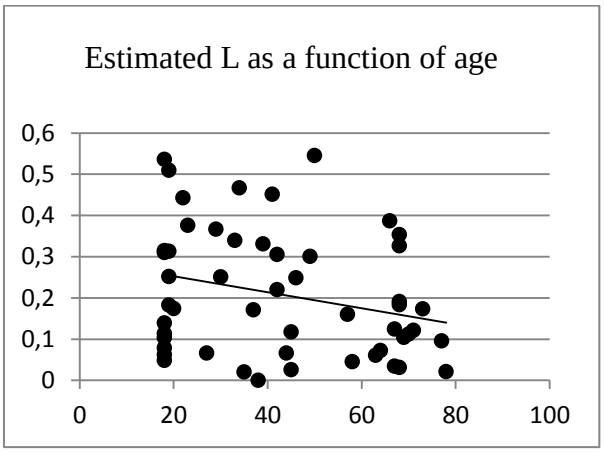
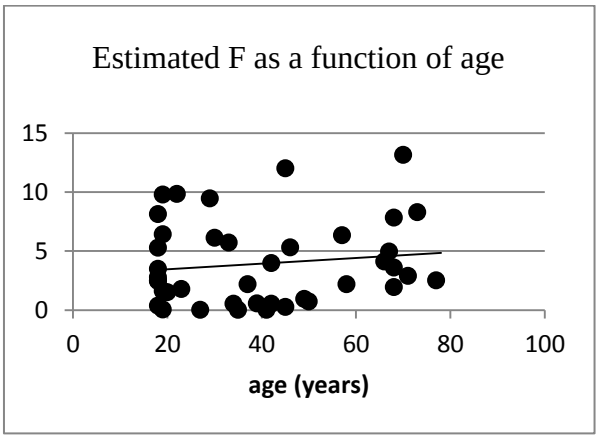



*Figure 2. Parameter estimates of an individual's Forgetting rate derived from Population Dilution model for each individual plotted as function of age.*




### 4.1. Evaluating statistical noise in the Warhol Task

Given that parameter optimization takes place in the context of a task that allows for guessing, some noise must be expected in the estimates derived thereby. It is possible that this is reflected in Figure 1. It is therefore necessary to establish that the wide variation observed in Figures 1 and 2 is genuinely attributable to individual differences between participants. To evaluate this, we developed an extensive Monte Carlo simulation in which 250 pseudo-subjects were simulated repeatedly with different, and pre-determined, values of ***L*** and ***F***. The data output from that simulation was then reoptimized for estimates of ***L*** and ***F*** in order to evaluate the variability intrinsic to the Warhol Task, which can be seen by comparing how closely the reoptimized values approximated to the original, predetermined, input values. For ***L***, this reveals

a mean deviation of 0.031 from the true value with a standard deviation of 0.057. In essence, this means that individuals differing by more than 0.114 can be assumed to be performing at significantly different levels. On that basis, most of the variations we observe in Figure 1 reflect genuine performance differences between participants rather than the outcome of chance.

The equivalent calculation of ***F*** is rather more involved because, as a reciprocal element in the basic model (pr=C/(C+E+ ***F***t)), the deviations from the expected value are heavily skewed towards overestimation. Further, when learning levels are low, smaller degrees of noise will drive the optimization falsely to boundary conditions (i.e. estimating ***F*** as 0 or infinity). This is because with very little learning, it is impossible to tell the difference between very high and very low levels of forgetting because they appear identical. Nevertheless, it has proven possible to demonstrate that the levels of forgetting observed between different participants do genuinely reflect different levels of performance. We can be reasonably confident that these individual differences reflect significant differences in performance.

## 5. CLINICAL POTENTIAL

### 5.1. Multivariate profiling of memory related deficit

Because the Warhol Task is aimed at detecting learning and memory related mild cognitive impairment, it is by necessity more complex than tests such as MMSE. The Warhol Task is rigorously quantitative, unlike the MMSE. For comparison, the MMSE provides an assessment of an individual's placement on a standardized distribution using performance measured by its 11 item questionnaire. Only 2 of these questions represent memory recall (Folstein et al., 1975). Whereas the PD model derives parametric estimates for multiple theoretical parameters representing underlying processes involved in memory and recall from 600 points of data across 5 tests. The Warhol Task's greater complexity has the virtue of being able to measure the finer details of memory on an individual level.

The greater volume of data collected in the Warhol Task provides a more comprehensive description of their ability to learn and recall sequential information. Building on this, detailed multivariate normative profiles can be established. The Warhol Task therefore places more emphasis on detailed quantitative profiles than cut-off points. That is in stark contrast to the MMSE, which has a threshold defining the point where performance is sufficiently low to be of clinical interest. Robust parametric statistical analyses can be used to establish a quantified level of certainty to an individual's distance from the average on specific multivariate profiles that are of clinical concern. This greater emphasis would lend better to a more deductive diagnostic mentality and towards monitoring incrementally across multiple observations (De Lepeleire & Heyrman, 1999). A drawback is that the Warhol Task currently takes 35 minutes to administer. But the potential for more detailed, sensitive, and accurate measurement of learning and memory related cognitive deficit arguably is worth the extra testing time.

### 5.2. Practical clinical utility

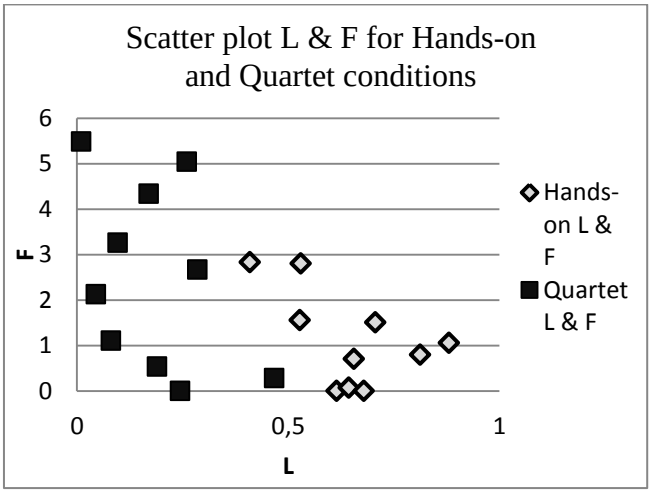
Bearing in mind the compilations that come with multivariate profiling it is therefore important to establish its practical application in a quasi-clinical setting before starting clinical trials. Moore (2013) administered the test to 17 long-standing volunteer patients of the Leicester General Hospital Sleep Clinic, all having received treatment for sleep apnoea (SA) for a minimum of 12 months and of average age 65.8 years and whose condition can be said to have stabilized. Other than commenting that the results were comparable to age-matched participants (implying a successful treatment outcome given the self-report of new patients) we do not elaborate on that study here. However, in this study, participants also undertook an additional short qualitative interview to examine the test complexity and the patient's attitudes towards it and its outcome in a clinical setting. This revealed no significant usability issues in the test; nor in the participant's inclination to take part in it. We do note, however, that because the test is necessarily challenging, it requires reasonably sensitive and skilled administrators to explain to the participants why this is necessarily the case and to maintain the patients cooperation and effort in undertaking it.

## 6. THE ROLE OF ERRORS IN MEASUREMENT

The most recent development in this line of research concerns both the aforementioned usability issues of the test, and the issue of confidence in estimates showing individual differences. Even though the participants of the quasi-clinical experiment described above reported no usability issues, it was believed a more effective version of the test in the Warhol Task could be devised. This innovative version, referred to as "Hands-on test", was designed to be more natural, quicker, and be a more theoretically exact test of *sequential* memory. More specifically, the Hands-on test requires that the participant, after the usual presentation and distraction part of the task, rearrange a second, identical, set of cans into the sequence they have just seen. This differs from the Quartet test by requiring the participants use their hands instead of interacting with computer software. Furthermore, the Hands-on test presents the participants with all the stimuli at once, rather than in sets of four. Finally the Hands-on test requires the participants reconstruct the whole sequence, not indicate where they thought each disconnected quartet was in a number line representing the sequence. While the Hands-on test differs in the way the participant interacts with the test, it is formally identical to the Quartet test in terms of the data it provides. The test in its Hands-on form becomes, arguably, more natural and less abstract.

We conducted an experiment to compare the effectiveness of both methods of testing. 10 participants conducted the Warhol Task and were tested with the quartet method, as described earlier, and 10 conducted the task and were tested with the hands-on method. This allowed a direct comparison of performance. The results found that the Hands-on test saw statistically significantly higher ***L***, t = 7.801, n = 10, df = 8, p = <0.005 (two-tailed), and lower ***F***, t = -1.881, n = 10, df = 8, p = <0.038 (two-tailed). The magnitude of difference in mean ***L*** between the Hands-on and Quartet tests, mean difference = 0.423, was substantial ($\eta^2$ = 0.772; Cohen, 1988). Likewise, but to a lesser extent, the magnitude of difference in mean ***F***, mean difference = -1.351, was strong ($\eta^2$ = 0.164). This is illustrated obviously in Figure 3, which shows the bivariate distributions for both test designs. It appears that the Quartet version of the test has been encouraging lower performance, making it more difficult to establish the legitimacy of individual differences when parameter estimates have been calculated.

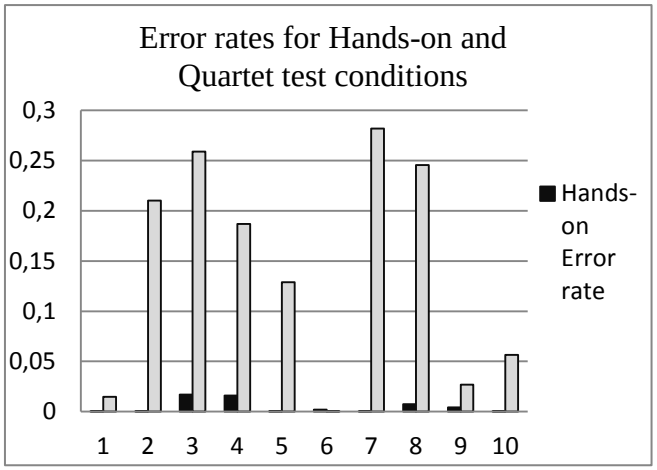
*Figure 3. The Learning and Forgetting rates for each individual in each test condition plotted on a scatterplot.*




Additionally we modeled a putative measure of error rate in these experiments. By this, we mean an estimate of the probability with which a sequence was uttered which the participant might otherwise, in perfect circumstances, have known was incorrect. Figure 4 illustrates the finding that error rates are significantly more frequent with quartet–style test (M = 0.141) as opposed to the Hands-on procedure (M = 0.005). Furthermore, there was substantial individual

differences in the higher rates of error seen in the Quartet test, SD = 0.109, in comparison to the Hands-on test, SD = 0.007. These two findings signify the possibility that high individual differences in error rates have been exaggerating the individual differences in learning rates. With this in mind, this experiment has revealed information about noise in the Warhol Task (PD model) that is introduced to the ***L*** and ***F*** parameter estimates at the very beginning, simply due to the usability of the test. The Hands-on test procedure is expected to be used in future experiments using the Warhol Task and represents a key development in creating a new test better suited to measuring individual performance and identifying deficits associated with learning impairment for use in a clinical setting.

*Figure 4. A bar chart showing the error rate for each individual across both tests.*




## 7. FUTURE DIRECTIONS AND CONCLUSION

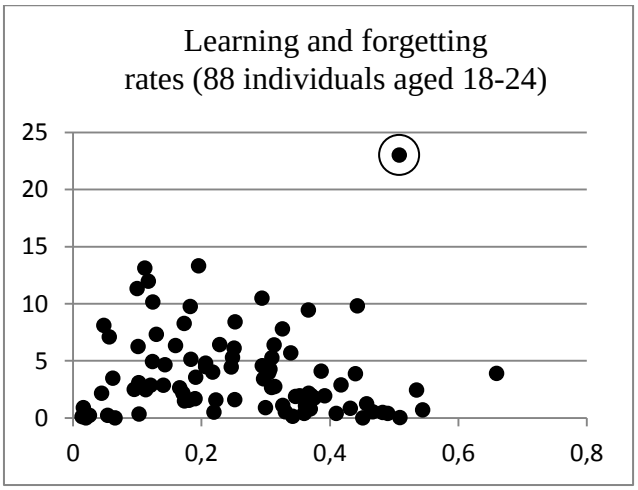
We have concentrated here upon the development of a test. Theoretical issues arising from this research are reported elsewhere. To date, we have: a) carried out an initial survey of performance in this test over the life span; b) developed techniques to establish the confidence levels in the results this provides; c) we have established the practical usability of the test in a, and outside of a, clinical setting; d) have identified conditions and performance levels where the test is problematic to interpret; and; e) have demonstrated very high levels of individual difference between participants carrying out the test; f) and that a portion of the individual differences were due to pollution in the test's data as a result of superficial usability of the test. We do not underestimate the technical difficulty of developing tests in this domain, where the reliable detection and quantification of mild cognitive deficit is a significant challenge.

Three key objectives, of many, are presently being focused upon to overcome this challenge. First, alongside the work previously described to establish confidence limits, a sufficiently large sample for each age group is required to establish normative levels within which the population at large can be expected to fall and against which individuals can be compared. Figure 5 illustrates the values of ***L*** and ***F*** for 88 participants of ages 18-24. This shows a) a general decline in forgetting rates with higher learning rates (a robust finding of some ongoing theoretical interest beyond the scope of the present chapter); b) substantial individual differences, as before, in both rates of learning and forgetting; but c) evidence of at least one participant (circled) whose forgetting rate is sufficiently high in comparison to the estimated learning rate to enable us to identify this as an outlier requiring further consideration.

Second, it is important to establish the test-retest reliability of this test as a precursor to longitudinal studies. At the time of writing, experiments are currently in progress to evaluate the degree to which the individual differences observed to date are preserved from one observation to the next. Third, and finally, we are planning a clinical trial of the test in a domain where mild cognitive impairment is to be expected; in this case in patients presenting for the first time to the

Sleep Apnoea Clinic at Leicester whose self-report and overt symptoms point towards mild to significant cognitive deficit (albeit usually reversible). These will be tested upon arrival and studied longitudinally over the onset of treatment. Such a trial will act both as a proof-of-concept (insofar as cognitive deficit is actually detectable in this group) and should also provide to the clinicians further information as to the degree and speed of recovery as a function of treatment.

*Figure 5. Scatterplot for learning and forgetting rates for each individual from a sample of 88 aged between 18-24.*

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