Statistical Power Analysis for PET Studies in Humans

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Although simple techniques have been established to determine statistical power when comparing, for example, the means of two groups of sampled data, the analysis is more complicated when establishing a trend in the data, such as with a linear regression. We present an approach to calculate the sample size necessary to reject the hypothesis that there is no trend in the data (slope is not different from zero) at a given level of statistical significance, given the intra- and inter-subject variability of the measurement. **Methods:** We have derived analytically the distribution of the t statistic, for a given non-zero slope, and integrated this distribution to determine in what fraction of trials a real trend in the population would be missed. We illustrate our approach by re-examining the issue of an age-related impairment in presynaptic dopamine metabolism as measured by PET. **Results:** We showed that the sample size necessary to determine whether 6-^{18}F-fluoro-L-dopa retention decreases with age depends critically on both the variability of the quantitative method used and on the magnitude of the expected change. **Conclusion:** The method we have illustrated is a simple statistical test that allows investigators to be certain that an experimental design has a sufficient sample size to demonstrate the effect under study.

Key Words: PET; sample size; statistical power

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The most commonly applied statistical tests estimate the probability that a given change or difference in measured data has occurred by chance, because of the vagaries of finite sampling, when no real difference is present in the population. A complementary technique, the analysis of statistical power, estimates the likelihood that a real difference in the population will be missed in a finite sample of a given size. This latter analysis is a crucial step in any experimental design, indicating the sample size necessary to observe a given difference or change in the data, with a known degree of certainty (*1,2*). Because the coefficient of variation (CV) of a measured quantity is often ill-defined or unknown a priori, particularly in experimental designs involving human subjects, this step is sometimes not feasible and is often over-looked. Although simple techniques have been established to determine statistical power when comparing, for example, the means of two groups of sampled data (*3*), the analysis is slightly more complicated when establishing a trend in the data, such as with a linear regression.

We derive analytically a simple test allowing investigators to be certain that an experimental design has a sufficient sample size to demonstrate the effect under study. In this article, we present an application of this statistical power analysis to a nuclear medicine investigation, using as an example the controversial question of presynaptic dopaminergic function and its change with normal aging. Despite the general concurrence of in vitro studies towards a gradual decline of the nigrostriatal pathway with age, the investigation of presynaptic dopamine metabolism using imaging techniques has yielded contradictory results.

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BACKGROUND

Anatomical studies indicate that the number of dopaminergic cell bodies in the substantia nigra declines linearly with age, at a rate of about 30,000 neurons (5%–6%) per decade (*4–6*). Reductions in neuron density in the basal ganglia with age (*7*), and age-dependent decreases in the volume of both caudate and lentiform nuclei in vitro (*8*) and in vivo (*9–11*) have also been demonstrated, suggesting that the basal ganglia are more affected by aging than the brain as a whole (*12*). Likewise, in vitro biochemical studies have demonstrated that dopamine concentrations in both caudate nucleus and putamen decline by roughly 10% of young adult levels per decade of adult life (*13–18*). Marked losses with age have also been reported for the activity of tyrosine hydroxylase (TH) (*4,19–24*) and dopa decarboxylase (DDC) (*4,20,21,24*), for vesicular monoamine transporter concentrations (*25*), and for dopamine uptake sites (*26–28*). In a study of 28 subjects between 17 yr and 103 yr, Kish et al. (*17*) found a modest decrease of about 5% per decade in DDC activity in caudate, but not putamen, and a decrease of roughly 10% per decade in dopamine levels in both caudate and putamen (*16,17*).

To study the integrity of presynaptic dopaminergic function in the human brain in vivo, the tracer 6-^{18}F-fluoro-L-dopa (F-dopa) has been used extensively (*29–31*). F-dopa traces the transport of large neutral amino acids across the blood-brain barrier, the activity of DDC and the storage and release of dopamine from the nerve terminal vesicles (*32–35*). A study by Snow et al. (*36*) established that F-dopa uptake rate constants are strictly proportional to cell densities in the substantia nigra, and therefore presumably give a faithful reflection of the number of surviving nerve terminals in the striatum.

Despite the known decline of the nigrostriatal pathway with age, the investigation of presynaptic dopamine metabolism with F-dopa has yielded contradictory results. The first indication of an age-related impairment in nigrostriatal function in vivo was presented by Martin et al. (*37*) in a study of 10 normal subjects using the F-dopa/PET technique. The presence of a modest aging effect was confirmed by this group in a separate longitudinal study of seven normal subjects (*38*), more recently in a set of 12 pairs of grandchildren and their grandparents (*39*) and finally in a thorough study of F-dopa/PET reproducibility in 10 normal subjects (*40*). These results have been contested by Sawle et al. (*41*) who found no significant correlations between F-dopa uptake and age in a study of 26 healthy volunteers (*41*). Likewise, no correlation with age was seen by Eidelberg et al. (*42*) in a study of 19 normal subjects by F-dopa/PET using a variety of analytical techniques, nor in a study of 21 normal volunteers by Murase et al. (*43*).

These discrepancies have generated heated discussion in the

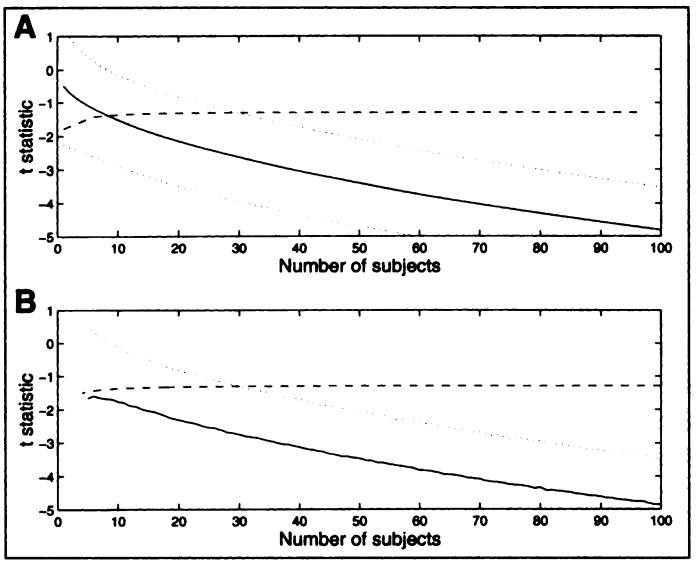

FIGURE 1. Expected value, confidence interval and significance level for *t* statistic. (A) Analytical results. The average *t* statistic expected for *n* between 1 and 100 is shown (solid line), along with the confidence interval around this value (dotted line); *t* would be less than the upper dotted line in 90% of trials. The dashed line illustrates values of *t* that would be necessary to reject, with 95% certainty, the null hypothesis that the slope, β is equal to zero. The intersection of the dashed and dotted lines indicates that 30 subjects are necessary to have a 90% chance of finding that *b* is significantly less than zero, under the assumption that the true value of β is −5% per decade. (B) Simulation results. The average *t* statistic computed from 10,000 trials per value of *n*, for *n* between 1 and 100 is shown (solid line), along with the 90th percentile of these values (dotted line); *t* was less than the dotted line in 90% of trials. The dashed line illustrates values of *t* that would be necessary to reject, with 95% certainty, the null hypothesis that the slope, β is equal to zero. These simulations are in excellent agreement with the analytical results shown in panel A.

literature (*44–48*). Several possible issues may be contributing these conflicting results, such as the position, size and shape of regions of interest (*47,48*), the inherent background noise in F-dopa/PET studies due to the presence of other labeled species in brain tissue (*35,49–51*), or the question of "usual" versus "successful" aging in normal subjects from an older population (*44–46,52*).

Another important issue is the sample size of the original studies, given intra-and intersubject variability in F-dopa uptake constants of up to 15% and 25%, respectively (*40,53–55*) [see Fig. 1 from Murase et al.'s article (43)], and the modest 5% or 10% decrease per decade that these investigations might be expected to demonstrate (*17*). As an example of the application of statistical power analysis in nuclear medicine, we investigated the sample size necessary to determine a trend with age in data acquired by the F-dopa/PET technique.

ANALYTICAL FORMULATION

Both anatomical and biochemical in vitro evidence suggest that the age-related decline in cerebral DDC activity is probably of the order of only 5% or 10% per decade. If we assume that our sample of the population has a uniform distribution in age, x, between 20 and 80 yr, then the expected value of the mean age, $\bar{x}$, will be 50 yr, and the expected value of the variance of x, σ_x^2, will be 300. In general, we can compute the expected value of $\Sigma(x\text{-}\bar{x})^2$ by considering that $\sigma_x^2 = \Sigma(x\text{-}\bar{x})^2/n$, and therefore

$$\Sigma(x - \bar{x})^2 = \sigma_x^2\, n \qquad \text{Eq. 1}$$

or $300n$ in this example.

Suppose that F-dopa uptake varies linearly with age, x, and let the uptake in a healthy 20-yr-old be equal to 100. We can then describe the expected F-dopa uptake, y', as:

$$y' = 100 - 0.5(x - 20), \qquad \text{Eq. 2}$$

assuming a linear loss of F-dopa uptake of 5% per decade. The measured F-dopa uptake, y, is then given by:

$$y = 100 - 0.5(x - 20) + \varepsilon \qquad \text{Eq. 3}$$

or more generally:

$$y' = \alpha + \beta x, \qquad \text{Eq. 4}$$

$$y = \alpha + \beta x + \varepsilon \qquad \text{Eq. 5}$$

where α is the y-intercept, β is the slope (here $\alpha = 110$ and $\beta = -0.5$), and the variable ϵ is an error term accounting for both inter- and intrasubject variations at a given age. We assume that the mean value of the error term, ϵ, is zero, and note that the variance of the error term, σ_ϵ^2, is therefore equal to $\Sigma\epsilon^2/n$.

From Equation 5, we can compute the mean value of y, $\bar{y}$, to be $\alpha + \beta\bar{x} + \epsilon$, which is equal to 85 if ϵ is zero. The expected value of the sum of squares, Σy^2, is likewise given by:

$$\begin{aligned}\Sigma y^2 &= \Sigma(\alpha + \beta x + \varepsilon)^2,\\ &= \Sigma(\alpha^2 + 2\alpha\beta x + \beta^2 x^2 + \varepsilon y' + \varepsilon^2)\\ &= (\alpha^2 + 2\alpha\beta\bar{x})n + \beta^2\Sigma x^2 + \sigma_\varepsilon^2 n + \Sigma\varepsilon y' \qquad \text{Eq. 6}\\ &= (\alpha^2 + 2\alpha\beta\bar{x})n + \beta^2(\sigma_x^2 + \bar{x}^2)n + \sigma_\varepsilon^2 n + \Sigma\varepsilon y'\\ &= (\alpha^2 + 2\alpha\beta\bar{x} + \beta^2\bar{x}^2)n + (\beta^2\sigma_x^2 + \sigma_\varepsilon^2)n + \Sigma\varepsilon y'\end{aligned}$$

and thus:

$$\begin{aligned}\Sigma(y - \bar{y})^2 &= \Sigma y^2 - (\Sigma y)^2/n\\ &= (\alpha^2 + 2\alpha\beta\bar{x} + \beta^2\bar{x}^2)n + (\beta^2\sigma_x^2 + \sigma_\varepsilon^2)n\\ &\quad + \Sigma\varepsilon y' - (\alpha + \beta\bar{x} + \varepsilon)^2 n^2/n \qquad \text{Eq. 7}\\ &= (\beta^2\sigma_x^2 + \sigma_\varepsilon^2)n + \Sigma\varepsilon y',\end{aligned}$$

which is equal to

$$= (\beta^2\sigma_x^2 + \sigma_\varepsilon^2)n \qquad \text{Eq. 8}$$

as long as the cross-correlation term, $\Sigma\epsilon y'$, is negligible, implying effectively that positive and negative sign errors are distributed uniformly across the age range. In an analagous way, the expected value of $\Sigma(x\text{-}\bar{x})\,(y\text{-}\bar{y})$ can be computed to be:

$$\Sigma(x - \bar{x})(y - \bar{y}) = [\alpha\bar{x} + \beta(\sigma_x^2 + \bar{x}^2) - \bar{x}\bar{y}]n \qquad \text{Eq. 9}$$

or in this example equal to $-150n$.

We performed a linear regression on n samples and estimated the slope of the regression line b. The best estimate of β, in a least squares sense, is given by:

$$b = \Sigma[(x - \bar{x})(y - \bar{y})]/\Sigma(x - \bar{x})^2, \qquad \text{Eq. 10}$$

and the variance of b is given by:

$$s_b^2 = [\Sigma(y - \bar{y})^2 - (\Sigma(x - \bar{x})(y - \bar{y}))^2/\Sigma(x - \bar{x})^2]/[n\,\Sigma(x - \bar{x})^2], \qquad \text{Eq. 11}$$

(*56*). A test of whether β is significantly different from zero can be performed by computing:

$$t = b/s_b. \qquad \text{Eq. 12}$$

When β equals zero, t is distributed as a Student's t statistic with $n-2$ degrees of freedom (*56*). This known distribution of t can be used in the standard way to reject the null hypothesis that β equals zero, given a computed value of b. Thus, if the computed value of t (Eq.12) is a large enough negative number, we can conclude that our random sample has passed the t-test, and that we have good evidence that β is less than zero. In practice, we choose a level of confidence (for example, 5%) and consult a table of the Student's t statistic to determine the value, T, that t must be less than to reject the null hypothesis.

For an analysis of statistical power, however, we consider the distribution of t that would be expected if β does not equal zero. In this case, a constant offset is added to each value of t (*3*), and the resulting distribution has an identical shape as the Student's t statistic with $n-2$ degrees of freedom, but is shifted along the t axis. Substituting Equations 1, 8 and 9 into Equation 11, we can compute the expected value of t, $\mathbf{t}$, as a function of n, and this expected value gives the magnitude of this constant shift. For the example illustrated, we find:

$$\mathbf{t} = 10b\sqrt{3}\sqrt{n}/\sigma_\varepsilon. \qquad \text{Eq. 13}$$

We have thus determined precisely the distribution of t, for a given nonzero value of β, and can integrate this distribution to determine in what fraction of trials, f, our computed value of b would fail the t-test, i.e., what fraction of the time would b not be considered significantly different than zero, even though β is non-zero, for samples of different sizes. We have demonstrated here that f is equivalent to the fraction of the time that the Student's t statistic with $n-2$ degrees of freedom is greater than $T - \mathbf{t}$, which can be computed easily or approximated from statistical tables:

$$f = P(t > T - \mathbf{t}), \qquad \text{Eq. 14}$$

where t is the Student's t statistic with $n-2$ degrees of freedom, and P indicates the cumulative probability function. Using these equations, T, $\mathbf{t}$, and $P(t > T - \mathbf{t})$ can be calculated for each value of n, and the sample size that gives the desired f value can be easily determined.

RESULTS

Intrasubject variation for F-dopa studies (both individual variations over repeated scans and measurement noise) can range from 2%–16% (CV), depending on the method of analysis (*40,52,54*). Intersubject variation for F-dopa uptake is between 5% and 23% (*54,55*), but these values include variation between subjects of all ages. For the following derivation we use estimates of 10% intrasubject variation in F-dopa uptake, and a further 15% intersubject variation, for healthy individuals of the same age. The s.d. of the error term is therefore equal to the square root of $10^2 + 15^2$, or about 18%; we model ϵ as distributed with mean 0 and s.d. 18; note that ϵ is not necessarily a normal variate.

Figure 1A illustrates the analytical results derived for $\sigma_\epsilon = 18$. For clarity, we have used a confidence level of 95% to determine T, the t value for which we conclude that β is significantly different from zero, and a 90% confidence level to determine f, the fraction of the trials in which we would like b to pass this t-test. The solid line in Figure 1A shows the average t statistic, $\mathbf{t}$, expected for n between 1 and 100. The dotted lines show how widely t is distributed around this value; t would be greater than the upper dotted line in 10% of trials. Mathematically, the upper dotted line plots the value u at which the cumulative probability $P(t > u - \mathbf{t}) = 10\%$, the lower line plots the value v at which $P(t > v - \mathbf{t})$ is 90%. The dashed line illustrates the values, T, that would be necessary to reject, with 95% certainty, the null hypothesis that the slope, β, is equal to zero.

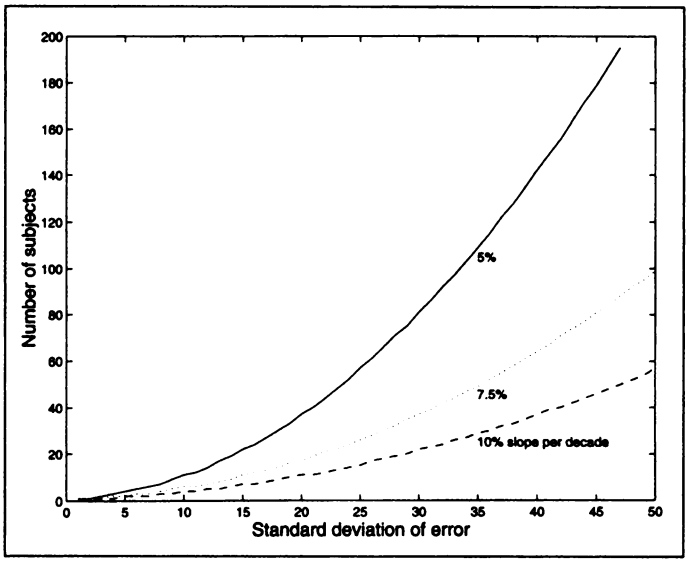

FIGURE 2. Number of subjects needed versus s.d. of the error term. The number of subjects necessary to have a 90% chance of finding b significantly different from zero are plotted against total inter- and intrasubject s.d., σ_ϵ, under the assumption that the true value of β is −5% (solid line), −7.5% (dotted line) and −10% (dashed line) per decade.

The intersection of the dotted and upper dashed lines in Figure 1A indicates the point at which $f = P(t > T - \mathbf{t})$ is 10%. This indicates that 30 subjects, uniformly distributed across the age range, are necessary to have a 90% chance of finding that β is significantly less than zero in this experiment.

We verified this result by performing a set of simulations. For each value of n between 1 and 100, we picked n subject ages, uniformly distributed between 20 and 80, using a multiple congruential random number generator (57). The expected F-dopa uptake value for each age was computed (Eq. 5), and a random error, ϵ, from a Gaussian distribution with mean 0 and s.d. 18 (*57*) was added. The best fit slope to the n uptake values and the t statistic for the trial were then computed according to Equations 10 and 12, respectively. This process was repeated using 10,000 trials per value of n. The solid line in Figure 1B shows the mean value of t obtained by this simulation method, the dotted line plots the 90th percentile of the distribution of t values at each n. These simulations are in excellent agreement with the analytical results shown in Figure 1A.

Finally, we repeated the analytical determination of sample size, varying the s.d. of the error term and the slope of the age dependence, β. The results of this analysis, for σ_ϵ between 1% and 50% and for slopes of 5, 7.5 or 10% per decade, are illustrated in Figure 2.

DISCUSSION

For the purposes of this study, we have assumed a modest, linear decrease in F-dopa uptake with age. While the number of dopaminergic cells in the substantia nigra declines linearly with age (*4–6*), changes in TH or DDC activity, dy, appear to be inversely proportional to age: $dy = A/x$, or equivalently, $y = A/x + B$, where A and B are constants (*4, 20*). This implies that the major changes in the activities of these enzymes occur before 20–25 yr, after which the decline is much less steep and may not be distinguishable from linear. For example, a rough calculation based on data illustrated in Figure 1 of McGeer and McGeer (*20*) shows a loss of about 70% of TH activity in putamen between 5 and 25 yr of age, but further losses of only 8% of values at 20 yr for each subsequent decade of adult life.

While none of the published F-dopa/PET studies of aging achieved samples of 30 subjects uniformly distributed across all decades from 20–80 yr, our estimate of the variance of measured values may be generous, in that we assumed a full 10% intrasubject variation, and that healthy normals of the same age could vary by a further 15%. The analysis of Vingerhoets et al. (*40,55*) indicates that the variance of the error term could be as little as $2^2 + 5^2$, which gives a CV of only 5.4%, and would imply that less than 10 subjects would be necessary to show a significant trend in the data. This low measurement variance is only possible, however, if simple ratio methods are used to quantify F-dopa retention, a technique which may not be appropriate for some research protocols. Since the investigation of presynaptic dopaminergic function with F-dopa is a well characterized technique, published inter and intrasubject variances for a given quantitative method can be used in a statistical analysis of power for most F-dopa/PET studies, and sample sizes may be chosen accordingly.

CONCLUSION

Our analysis strongly supports the common sense suggestion (*55*), that analytical methods be chosen with care to address the issue under study by the most appropriate means. The method we have illustrated here is a simple statistical test which allows investigators to be certain that an experimental design has a sufficient sample size to demonstrate the effect under study. We concur with other groups (*1,2*) in suggesting that statistical analyses of power could more routinely be used in nuclear medicine research protocols.

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